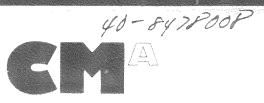
Microfiche No.					240000
wicronicha No.	OTS051	2376			
New Doc I.D.		an the contractive of the contra	Old Doc I.D.	katalahakakakakakakakakakakakakakakakakakak	
	40-8478008			42062 B2-6	0
Date Produced	5/30/84	Date Recieve	ed	TSCA section 4	Saline
Submitting Organization	on CI	HEM MANUF	ASSOC		
					-
Contractor			akala da	alarkalarkalarkalarkalarkalarkalarkalar	
Contractor	EASTMAN KODA	AK CO			To a company of the c
Document Title		orthe with work position to the collection that and an eller still a still a still a still a still a still a s	tir dir Ardente direkte da direkte dir	inde strekte destaste destaste destaste destaste destaste desta trada desta desta desta desta desta desta desta	Series Series
	STUDIES WITH TED 053084	GLYCOL M	ONOBUT : ETHER	WITH COVER	motoration manage consider
					Siedióssippopopopopo
					Application of the Particular
					Selection of the Assessment species
					** HEROSTATA CONTINUES AND
					Nazaza.
Chemical Categ	and a manufacture of the control of		merena sangatusti atauputantan kenis siren siri. Bathadi ahadi ahadi ahadi ahadi ahadi ahadi ahadi ahadi ahadi	rensentatutataitaihakidadakin haladalah da	- Section Section 1
DGBE & DO	5BA				SHALD MINISTER SEGRECATION OF A SHALL SHAL



## CHEMICAL MANUFACTURERS ASSOCIATION

May 30, 1984

### BY HAND

Mr. Gary Timm
Director
Office of Pesticides and
Toxic Substances
Environmental Protection Agency
Room 421-East Tower
401 M Street, S.W.
Washington, D.C. 20049

RE: Diethylene Glycol Monobutyl Ether

Dear Mr. Timm:

The Glycol Ethers Program Panel of the Chemical Manufacturers Association submits the enclosed studies on diethylene glycol monobutyl ether (DGBE). These studies include:

- Acute Oral LD<sub>50</sub>

- Acute Dermal LD<sub>50</sub>

- Six Weeks Repeated Dose

- Five Weeks Repeated Vapor Inhalation

- Short-Term Reproductive Toxicity

(Eastman Kodak);

(Eastman Kodak);

(Eastman Kodak);

(Dow Chemical); and

(NIOSH)

The Panel will continue to collect available toxicological data on DGBE and share this information with you.

Please do not hesitate to call me at 887-1198 should you have any questions.

Sincerely,

Lori M. Ramonas, Pn.D.

Manager

Glycol Ethers Program

Or Paus Price

TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER  $\hbox{ I. ACUTE ORAL $LD_{50}$ }$ 

Eastman Kodak Company

April, 1984

TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER

1. ACUTE ORAL LD<sub>50</sub>

## Introduction

Available data indicate that the glycol ethers, in general, have a low to moderate degree of toxicity. The majority of these compounds are only slightly irritating to the skin, though most are readily absorbed percutaneously. Eye contact produces moderate irritation. Prolonged or repeated inhalation of the vapors may cause irritation and adverse systemic effects; however, the relatively low volatility of these ethers should prevent exposure to toxic concentrations at normal temperatures. (1)

Several toxicity studies were designed in our laboratory to specifically study the toxicity of diethylene glycol monobutyl ether (DB). This report describes the results of acute oral  ${\rm LD}_{50}$  studies in rats and mice.

## Materials and Methods

The test compound was supplied by the Texas Eastman Company. An aliquot of each test sample was submitted to the Kodak Park

Industrial Laboratory for identification of contaminants. Gas

chromatographic analyses showed that the test compound was > 99.5% pure. The chemical structure of DB was confirmed by infrared spectroscopy.

The test species were Charles River COBS, CD, BR male rats (150-200 g) and Charles River, COBS, CD-1 male mice (15-17 g). The animals of both species were received from the same supplier at the same time. All animals were quarantined and acclimated in our laboratory prior to being randomly assigned to the study. Two batches of both species were received approximately two months apart. The acute oral  ${\rm LD}_{50}$  was determined in fasted and fed animals, with a period of two months between experiments. Each series of  ${\rm LD}_{50}$  determinations (fasted and fed) in both species were conducted exactly the same except for the fasting prior to dosing and the batch of animals used.

Twenty-five animals of each species were divided into five dose groups of five rats or mice each. The doses given were calculated on a mM/kg basis for the purpose of comparison with other compounds and ranged from 10.5 to 168 mM/kg progressing by a factor of two.

Dose administration was by gavage, undiluted, using a glass syringe fitted with a polypropylene catheter. The animals were individually housed in suspended wire-bottom cages. Water was available ad libitum and except for the removal of the food from the fasted animals 16-20 hours prior to treatment, food was available ad libitum.

General appearance and activity, pharmacologic and toxicologic signs and mortality were checked twice daily except on weekends and holidays. The appearance of stools and urine on the trays was noted and individual body weights were done prior to dosing and at the end of the two week observation period.

Animals that died during the study and all survivors were necropsied and examined for gross pathology. The survivors within a particular compound group were necropsied by the same prosector beginning with the high dosed animals and proceeding to the low dosed groups. The  ${\rm LD}_{50}$  with its 95% confidence interval was calculated using the method of Thompson and Weil.  $^{(2)}$ 

#### Results and Discussion

Acute oral  ${\rm LD}_{50}$  values for DB in fasted male rats and mice and fed male rats and mice are presented in Table 1. These results are in agreement with reports in the literature which indicate that the mono ethers of diethylene glycol have a low degree of acute oral toxicity.  $^{(1)}$ 

In both species, DB was less toxic in the fed animals, and was more toxic for mice than for rats in both fasted and fed animals.

Clinical signs of toxicity for both fed and fasted animals of both species were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration and death. Deaths occurred from within one to four days following treatment. Hematuria was not observed at any dose level of DB in either species.

No compound-related effects were observed on gross autopsy.

## References

- Rowe, V. K., Derivatives of Glycols, Chapter XXXVI in Industrial Hygiene and Toxicology, Vol. II, 2nd Edition, F. A. Patty, Ed., pp. 1537-1592, Interscience Publishers, Inc., 1963.
- Thompson, W. R. and Weil, C. S., On the Construction of Tables for Moving Average Interpolation. <u>Biometrics</u> 8:51-54, 1952.

Table 1. Acute Oral LD50's of Diethylene Glycol Monobutyl Ether in Fasted and Fed Rats and Mice

Animal	LD <sub>50</sub> (mmol/kg)	LD <sub>50</sub> (mg/kg)
Rat (fasted)	45.0 (32.1 - 63.2) <sup>a</sup>	7292 (5200 - 10238)
Rat (fed)	59.4 (40.1 - 87.9)	9623 (6496 - 14240)
Mouse (fasted)	14.9 ( 9.1 - 24.2)	2406 (1474 - 3920)
Mouse (fed)	34.1 (22.0 - 52.9)	<b>5526 (3564 - 8</b> 570)

a 95% confidence interval

TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER  ${\tt II.~ACUTE~DERMAL~LD}_{50}$ 

Eastman Kodak Company
April, 1984

TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER

## Introduction

Available data indicate that the glycol ethers, in general, have a low to moderate degree of toxicity. The majority of these compounds are only slightly irritating to the skin, though most are readily absorbed percutaneously. Eye contact produces moderate irritation. Prolonged or repeated inhalation of the vapors may cause irritation and adverse systemic effects; however, the relatively low volatility of these ethers should prevent exposure to toxic concentrations at normal temperatures. (1)

Several toxicity studies were designed in our laboratory to specifically study the toxicity of diethylene glycol monobutyl ether (DB). This report describes the results of acute dermal LD $_{50}$  studies in rabbits and acute skin irritation studies in guinea pigs.

The skin irritation studies in guinea pigs were done in the Toxicology Section, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

The test compound was supplied by the Texas Eastman Company.

An aliquot of the compound was submitted to the Kodak Park

Industrial Laboratory for identification of contaminants. Gas

chromatographic analyses showed that the test compound was > 99.5%

pure. The organic structure of the compound was confirmed by

infrared spectroscopy.

Male New Zealand white rabbits were purchased from Dutchland
Laboratory Animals Inc., Denver Pa. The animals were randomly
assigned to groups of five rabbits each using a computerized
randomization process. Each animal was assigned a unique
identification number and housed individually in a metal cage marked
with the animals's number. Purina Laboratory Rabbit Chow® and
drinking water were available ad libitum.

The rabbits were quarantined and acclimated to the laboratory conditions for at least three weeks prior to treatment. During this period each animal received a health status examination by a staff veterinarian.

The test compound was administered to the closely clipped, unabraded back of the animals. Depending on the volume to be administered, one or more  $3\ 1/2\ x\ 4$  inch Werbil® Handi Pads were held in close

contact to the skin by an occlusive wrap of dental dam. The compound was injected under the wrap into the pad using a long stainless steel intubation needle. The edges of the dental dam were then sealed using adhesive tape. The doses were administered on a millimole per kilogram of body weight basis to facilitate the comparison of  $LD_{50}$ 's with other compounds. The following four dose levels were administered; 10.5, 21.0, 42.0 and 84.0 mmol/kg (1701, 3402, 6804 and 13608 mg/kg).

After 24 hours, the wrap was removed, the amount of any residual compound was estimated and the area was wiped with cotton to preclude further absorption.

All animals were observed twice daily for mortality and once a day for abnormal signs. Dermal responses were noted and scored on days 1, 3, 7, 10 and 14 using the method of Draize. (2) Individual body weights were recorded prior to dosing, on day 7 and at death or termination (day 14). Survivors were killed on day 14 with an overdose of sodium pentobarbital, exsanguinated and autopsied. Animals that died during the observation period were autopsied also. Gross pathology was recorded for all rabbits. The LD<sub>50</sub> was calculated using the method of Thompson and Weil. (3)

Primary skin irritation was determined by application of the compound to the depilated abdomen of the guinea pig at a dose of 1, 5, 10 or 20 mL/kg under an occlusive wrap for 24 hours.

#### Results

The acute dermal LD<sub>50</sub> of DB for the rabbit was 17.06 mmol/kg with a 95% confidence interval of 12.9 to 22.5 mmol/kg. This is equivalent to 2764 mg/kg, with a 95% confidence interval of 2090 to 3645 mg/kg.

Clinical signs of toxicity noted after treatment were death, anorexia, depression, tremors and prostration.

The skin reactions in the rabbit, evaluated and scored according to the Draize method, indicate that DB produced only slight irritation. When skin irritation was determined in the guinea pig by the standardized procedure used in our laboratory, DB produced only slight irritation. Table 1 presents the dermal irritation response for DB in the rabbit and the guinea pig. The dose associated with the irritation is the highest dose given at which enough animals survived so that irritation could be evaluated.

Gross pathology at autopsy is summarized in Table 2. Some evidence for adverse effects on the kidneys was noted, particularly at the higher dose levels. Reddish colored fluid was observed in the primary bladder of the second lower dose group. No such findings were noted at either of the two higher doses. Edematous and hemorrhagic lesions of the thymus were observed at the higher doses.

## References

- Rowe, V. K., Derivatives of Glycols, Chapter XXXVI in Industrial Hygiene and Toxicology, Vol. II, 2nd Edition, F. A. Patty, Ed., pp. 1537-1592, Interscience Publishers, Inc., 1963.
- Draize, J. H., Dermal Toxicity Appraisal of the Safety of Chemicals in Food, Drug and Cosmetics, pp. 46-59, 1959.
- 3. Thompson, W. R. and Weil, C. S., On the Construction of Tables for Moving Average Interpolation. Biometrics 8:51-54, 1952.

Table 1. Skin Response of Rabbits and Guinea Pigs to Topical Application of Diethylene Glycol Monobutyl Ether

Dose <sup>a</sup> (g/kg)	and the second s	Irritationb
3.4		Slight
19.1		Slight
	3.4	0se (g/kg) 3.4

<sup>&</sup>lt;sup>a</sup> Highest dose at which sufficient animals survived for evaluation.

b Irritation in rabbit according to Draize; guinea-pig according to our laboratory standard procedure.

Table 2. Summary of Gross Pathology Examination in Rabbits

Diethylene Glycol Monobutyl Ether

~	-	-			
	10.5	- Dose (1)	amo1/kg) -	84.0 -	Total
No. Rabbits Examined:	5	Ë	<b>5</b>	5	20
No. survivors to 14 days	5	1	ΰ	0	б
Thymus Edematous Edema & hemorrhage Increased vascularity Yellow discoloration		3	2	3	2 3 2 3
Lungs Brown discoloration		2			2
Liver Brown discoloration		2			Zia.
Kidneys Enlarged Discoloration (tan) Pelvis discolored		1 2 2	1		2 2
Stomach Hemorrhage		3			<b>3</b>
Small Intestines Increased vascularity			1		g.
Urinary Bladder Fluid, dark red		3			3
Skin Reddened areas			4	#F	9
Thoracic Cavity Brown fluid		2			2
Fat Tinged - yellow		3			3

# TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER III. SIX WEEKS REPEATED DOSE STUDY

Eastman Kodak Company
April, 1984

TOXICITY STUDIES WITH DIETHYLENE GLYCOL MONOBUTYL ETHER

III. SIX WEEKS REPEATED DOSE STUDY

## Introduction

The ethers of ethylene and diethylene glycol have been extensively used in industry for the past 15 to 40 years. Available data indicate that the glycol ethers, in general, have a low to moderate degree of toxicity. The majority of these compounds are only slightly irritating to the skin, though most are readily absorbed percutaneously. Eye contact produces moderate irritation.

Prolonged or repeated inhalation of the vapors may cause irritation and adverse systemic effects; however, the relatively low volatility of these ethers should prevent exposure to toxic concentrations at normal temperatures. (1)

Several studies were designed in our laboratory to specifically investigate the toxicity of diethylene glycol monobutyl ether (DB). This report describes the results of a six week repeated dose (gavage) study in male rats.

#### Materials and Methods

The test compound was supplied by the Texas Eastman Company. An aliquot of each test sample was submitted to the Kodak Park

Industrial Laboratory to be analyzed for purity and verification of molecular structure. Gas chromatographic results showed that DB was > 99.5% pure. The molecular structure of the compound was confirmed by infrared spectroscopy.

Doses of 3564, 1782 or 891 mg of DB per kilogram of body weight equivalent to 1/2, 1/4 or 1/8 the acute oral (fasted) LD<sub>50</sub> determined in our laboratory were administered undiluted by gavage, five days per week for six weeks. This schedule provided 29-33 doses over a 44 day period. The control animals were handled similarly to the treated rats except that they received a volume of distilled water, equal to the largest volume given a treated animal. All doses were recalculated weekly to adjust for changes in body weights.

The animals were housed individually in suspended wire cages and Purina Rodent Chow 5001° and water, via an automatic watering system, were available ad libitum.

Individual body weights were recorded on days 0, 3, 6, 13, 20, 27, 34 and 41 of the study. Individual animal feed consumption data were recorded at the time the animals were weighed.

Animals were observed daily, except on weekends, for clinical signs of systemic toxicity and for deviations from normal with respect to general appearance and behavior. The appearance of urine and feces on the dropping trays was noted. Mortality was checked daily.

Blood was drawn from the inferior vena cava just prior to autopsy for hematologic and serum clinical chemistry determinations. These determinations consisted of hemoglobin concentration, hematocrit, red blood cell counts, red cell indices, total and relative white cell counts, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, urea nitrogen, creatinine and glucose.

Animals that died spontaneously were autopsied as soon as possible and moribund animals were euthanized with  ${\rm CO}_2$  and autopsied. Tissues were collected for histopathologic examination.

At termination, the survivors were killed by CO<sub>2</sub> inhalation and the following tissues were collected, fixed in 10% buffered formalin, processed by standard histologic techniques and examined by light microscopy: lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach, cecum, colon, duodenum, jejuneum,

ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes, epididymides, prostate, seminal vesicles, coagulating gland, bone marrow, tongue and nasal cavities. Eyes were fixed in Zenker's solution. Prior to being sectioned for fixation the liver, kidneys, heart, testes, brain and spleen were carefully trimmed and weighed for organ/body weight comparisons.

#### Results and Discussion

## Mortality

The disposition of all animals on the study is shown in Table 1. No significant compound related mortality occurred in any dose group.

#### Body Weight and Feed Consumption

Individual body weights and feed consumption data with means and standard deviations, are listed in Tables 2 and 3. These data are presented graphically in Figures 1 and 2. Only the high dose of DB produced significant reductions in body weight gain and feed consumption. The intermediate and lower doses of DB produced slight, statistically non-significant, reductions in mean body weight gain.

## Hematology and Clinical Chemistries

The individual values of the hematologic and serum clinical chemistry determinations are presented in Tables 4 and 5, respectively. The major hematologic effects produced by the test compound were effects on the red blood cells.

Diethylene glycol monobutyl ether (DB) decreased hemoglobin concentration and total red cells at the high and intermediate dose levels. Calculated red cell indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), reflected abnormal red cell morphology (microscytosis, macrocytosis, hypochromasia). The high and intermediate doses of DB increased MCV and MCH and decreased the MCHC.

The high and intermediate doses of DB produced significant decreases in the glucose level. This change, though statistically significant, was only slightly different compared to the controls and its toxicologic significance is uncertain.

## Organ/Body Weight Comparisons

The individual terminal body and organ weights are presented in Table 6.

Significant reductions in mean terminal body weights were seen at all dose levels of DB.

Absolute and relative spleen weights of the animals given the high and intermediate doses of DB were significantly increased. The high and intermediate doses of DB significantly increased the absolute and relative weight of the liver.

Other organ weight changes noted were a reflection of the decreased body weight gain seen in these groups.

#### Clinical Signs

The high dose of diethylene glycol monobutyl ether (DB) produced bloody urine and blood around the nose and mouth in one rat after 23 days on the study. Other clinical signs noted at this dose level were dyspnea, prostration, and unkempt hair coat. No clinical signs of toxicity were seen at the intermediate and low dose levels.

## Gross and Histopathology

Blood was seen in the urinary bladder of some animals from the high dose group of DB that died prior to termination and dark, enlarged spleens were seen in some of the survivors. No abnormalities were noted in the intermediate and low dose animals of DB.

Histopathologic lesions are listed in Table 7. All doses of DB produced hyperkeratosis of the stomach and acanthosis of the stomach was seen in a few animals.

Splenic congestion and red pulp hypocellularity and hemosiderin-like pigmentation were seen at the high dose of DB.

Histologically, renal effects included hyaline droplet degeneration, proteinaceous casts, and hemosiderin in the proximal convoluted tubules. The proteinaceous casts and hemosiderin appeared to be compound related but may have been secondary to the hematologic effects. The hyaline droplet degeneration was also seen in all ten control rats. Thus, the significance of this finding is uncertain.

#### Conclusions

No spontaneous deaths were observed in any of the dose groups. Two animals receiving the high dose were euthanized because of their moribund condition.

A statistically significant depression in body weight (22%) and food consumption (20%) was observed for animals receiving the high dose.

For the low and intermediate dose groups, body weight and food consumption were not significantly different from those of the control animals.

Significant compound related histopathology was found in the spleens of DB treated rats. This consisted primarily of splenic congestion in 6/10 rats at the high dose only. Red pulp hypocellularity, hemosiderin and extramedullary hematopoiesis were also present in some animals at the high dose.

Kidney effects included proteinaceous casts in the proximal convoluted tubules. Hyaline droplet degeneration was seen in all test groups and in all control animals and was not considered to be treatment related.

No effects were seen on absolute testes weight or on testicular histopathology. Organ weight effects included increased absolute and relative liver and spleen weights at the high and intermediate doses.

Hematologically, significant decreases in red cells and hemoglobin were seen after treatment with DB, but only at the high dose level.

No effects on clinical chemistry were noted.

## References

 Rowe, V. K., Derivatives of Glycols, in "Industrial Hygiene and Toxicology, Chapter XXXVI, Vol. II, 2nd Edition, F. A. Patty, Ed., pp. 1537-1592, Interscience Publishers, Inc., 1963.

Table 1. Repeated Dose Study with Diethylene Glycol
Monobutyl Ether in Rats - Disposition of Animals

	### The Part of th		errenen valet er engensson governet ernet ekkennigen omfantaliste kindstylle de til til ett ett ett ett ett et	· A
Dose in mg/kg (mmol/kg)	Spontaneous Deaths	Moribund Sacrifice	Intubation Error	Killed at Term
3564(22)	0	2	4	4
3304(22)	Ü	tio .	***	adj
1782(11)	0	0	2	8
891(5.5)	0	0	1	9
Control <sup>a</sup>	0	0	0	10

a Received a volume of distilled water equal to the highest volume given to a treatment group.

Table 2. Body Weights (g)

DODY REIGHT	DIE	imtene of	COL NOVOB	UTYL ETHER	(03) 22	180L/X0 -		
RAT	DAY O	BAY 3	BAY 6			SAY 87		DAY 41
1	237	221	246	290	279	* 238	230	205
802	237 229	221 226 205	234				272	299
183 184	221 257	305	234 253	243 310	236 311	<b>34/</b> 6	876	82 A A
105	240	appropriate man						
106	214	199 246	207	262 257	\$59			
197 198	241 217	199			943	273 326	259	292
107	224	210		207	270	326	337	<b>?</b> _ 6
190	231							
ALM	991 4	214 9	229 8 *	276.6 <sup>8</sup>	274. 8 <sup>8</sup>	304. đ <sup>5</sup> 23. 7	312.0*	316.0*
8. D.	13.0	16. 9	26.4	19.3	22. 1	23.7	25.0	23. 9
BODY MEIGHT						MOL/KG DAY 27	nav al	nav ši
RAT	DAY O							
191	262	275	263	322	322	349 343	372	395
192	221	246	249	306	233	343	38a	392
193	252 245	98.	978					
194 193	242	256 25 <b>9</b>	276	312	323	354	346	366
196	258	271	288	329	343	369	367	414
197	216	271 271 226	244	277	271	314	337	354
198	221	<b>&amp; &amp; J</b>	244	329 277 267 277	291 291 291	314 304 325	344	365
199	217	<b>329</b> <b>3</b> 54	247	303	224	341	370	263
200					4444			
AVQ	236.8	248.0	267.0	299.4	313.0	343. i 24. 7	361.4	380 I
5. 0.	17.5	17. 2	17.2	22. 🕈	22.4	24.7	32.1	& h . /
SODY MEIGHT						5 MMOL/KG DAY 27	DAV ZA	DAY A1
RAT		DAY J	DAY &	300 A 8 %	MA SA	Start A SE &	20 A 20 A	Marked K. A. M.
201	530 534		260	~~	<b>**</b> * <b>**</b>	244	370	300
303	230	244 236	235	300 270	71¢	343		
203 204	204	219	237	240	@ & A	900	304	320
	241	257	277	217	322	341	201	401
204	233	246	264	276	307	240		371 383
207	233	234	273 •		314	348 378	307	421
208	240	263	202 231	32.1	240	West - Galler	342	
209	210	234 235	234	243		465, 114, 105,	May . Our	
W. U. 42								ga 10 A 10
AVO	227. 3	243.3	261.4	296.4	300.1	340, 8 25, 0	337. 2	374. 7 28. 8
9, 9.	11.3	13. 7	14. 2	18. 2	<b>30.</b> 8	<b>€3.</b> ♥	€0.	100 mm · 200

<sup>\*</sup>Statistically significant p <0.05

Table 2 (cont.). Body Weights (g)

						8		
DODY WEIGHT			CONTROL					The medical committees
RAT	DAY O	DAY 3	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41
271	<b>259</b>	236	261	283	304	339	363	374
272	. +7	<b>Z</b> J7	a L D	370 290	356 311	342	356	381
273	211	29 <u>4</u> 530	256 21.3	329	342	375	406	#10 
274 275	257 207	516	204	266	271	<b>3</b> 03	316	ÕĈĒ
COLUMN TO SERVICE DE LA COLUMN	<del></del>	6/6-	E	768	341	374	406	4.2
277	252	266	276	307	330	363	379	400
275	234	259	£77	366	: 345	372	347	5 7 4
279	248	276	292 -	- 350_	372	416	440	455
285	6 15 3	845	253	304	316	353	383	N. S.
AVG	234 6	253.3	Z72 0	31.1.4	727 8	757 7	JE7 3	70 5
S D	17.3	196	18 6	25 1	29 1	31.3	36 3	
enegativosamposa <u>nte</u> energiande de desprincipales de desprincipal			rausensstamistation (************************************				akiling Siden Liberhee ASSI-1000 VISS 419 Public Et 2000	
M WOOLANDS WE COMPOSED AND COMPANY		er respekt sitt i <del>ette stad sitten i op en en en elde st</del> or ette ette en en en en elde stad en en elde stad ett			National Control of the Control of t			a markan dia mada mada mada kalan markan dalam (a
					ili do de la filla de la facilita d	g.		
							Name of the Control o	SAME THE PARTY OF
and control of the same of	or commence of the second	<u>Orangogiada formaja antikana da battina arter (b.133 arter 1513</u>	and the second s	The second secon			transfer Property (1987) property processes amond many abundantacharache (1980) (1984) (1984) (1984)	the and the control of the control o
			engen og grande state og skippelikke providels menne, selveke er skilde er skilde melle melle melle melle mell I skilde s			and a parameter of the second and th		
	COP TO COMPANY TO THE STATE OF	agenting geographic and an experience of the control of the contro			basest = miljoritist propriest part envelope accomply postporprocesses a mount			
		gggggggggggggggggggggggggggggggggggggg						

Table 3. Feed Consumption (g/rat/day)

							7	-	
	THE REAL PROPERTY AND ADDRESS OF THE PERSON NAMED IN COLUMN TO THE					:	\$ & \$-		
FEED (	DNSUMPT	ION	DIE	THYLEKE GL	ACUT MONIOR	UTYL ETHER	(08) 82	PMOL/KG	
*	RAT	đạy	#3 W	DAY 6	DAY 13	DAY 20 .	DAY 27	DAY 34	DAY 41
	181	10	7	. 16 2	20 5	19 0	50 8	20.4	20 5
	152	12.		17 3	4 F.	16 1	18.0	18 5	18 6
	103 164	9. 10	and the Participation of the P	15 C	s. à	61	8 4. 6	\$ 46 . db.	86 9
	185	9 4	~						
	156	0.		10.8	47 -	16 1	18.6		
	187	14 7.		8 7 12 0	151	17.6	18.3		75.4
	192 199	11		17 0	21 0	20.3	20 8	20 B	£'0 4
THE PROPERTY AND PROPERTY OF THE PROPERTY OF T	190			STATE OF THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS NAMED IN C		COTOM CONTRACTOR OF THE PARTY O			
Street, place of the second second	AVG	10	47 *	14.00	77 IJ*	1E 40*	19.30*		1= 4:
	S D		37	3 14	£: 11	1 17	1 39	172	1 11
VEFN V	CONSUMPT	PAY	ama di manana manana Manana manana manan	DV.Y &	D: V 13	TAY 20	DAY 27	DAY 34	Day at
				1 1 A 1 7 85	£14. 1 3 3		We had a filter	Section 1	2
	RAT			econnection removement consideration of the best of			EFE (EFE 15)	~ × .	and the same of th
	191	20	7	21 7		55.8	22.8	23 4	24 0
	191		7	econnection removement consideration of the best of	52 8	22 8	22.8	23 6	
	191	20 23	7 3	21 7 24.0	5'2'	25.5			
	191 192 193 194 195	20 23 16 17	7 3 3	21 7 24.0	5 2 2	25.5	22 6	20 0	20 0
	191 192 193 194 195	20 23 16 17	7 3 3 3	21 7 24.0 17.2 20.2	5'	25.5			
	191 192 193 194 195 196 197	20 23 16 17	7 3 3 9	21 7 24.0	5 2 2	25.5	22 6	22 3 22 5 21 6	20 0
	191 192 193 194 195	20 23	7 3 3 9 9	21 7 24 0 17 2 20 2 22 2 18 7 24 0 18 8	20 2 21 14 5 22 3 20 2	25. 5 22. 0 23. 7 20. 2 41. 3 20. 9	22 6 23 8 20 7 21 8 21 1	22 3 23 4 21 6 21 7	20 0
	191 192 193 194 195 196 197	20 25 16 17 21 16	7 3 3 3 0 7	21 7 24.0 17.2 20.2 22.2 19.7	82 9 82 9 83 6 84 9	25. 5 22. 0 23. 7 20. 2 21. 3	22 6 43. 2 20 7 61. 8 21. 1 23. 2	22 3 22 5 21 6	20 0
	191 192 193 194 195 196 197 198 199	20 25 16 17 21 16 16 17 21	7 3 3 3 0 7 0 7	21 7 24.0 17.2 20.2 21.2 18.7 24.0 19.8 21.8	20 9 21 2 44 5 20 2 20 2	29. 5 22. 0 20. 2 20. 2 20. 9 20. 9 22. 7	22 6 43. 2 20 7 61. 8 21. 1 23. 2	22 3 23 7 21 6 21 7 22 8	20 0
	191 192 193 194 195 196 197 198 199 200	20 25 16 17 21 16 16 17 21	7 3 3 3 0 7 0 7	21 7 24.0 17.2 20.2 21.2 18.7 24.0 19.8 21.8	20 9 21 1 14 5 20 2 20 2	25. 5 22. 0 25. 2 20. 2 21. 0 20. 9 22. 7	22 6 43. 2 20 7 61. 8 21. 1 23. 2	22 3 23 4 21 6 22 4 21 7	20 0
FEED	191 192 193 194 195 196 197 198 199 200	20 23 16 17 21 16 16 17 21	7 3 3 3 0 7 0 7 0 7	21 7 24 0 17 2 20 2 21 2 18 7 24 0 19 8 21 8	20 9 20 2 23 4 14 5 20 2 20 2 20 2	29. 5 22. 0 20. 2 20. 2 20. 9 20. 9 22. 7	22 6 23 2 20 7 21 8 21 1 23 2 22 70 1 70	22 3 23 4 21 6 22 4 21 7 44 6	20 0
FEED	191 192 193 194 195 196 197 198 199 200	20 23 16 17 21 16 16 17 21	7 3 3 0 7 0 7 0 7 0	21 7 24 0 17 2 20 2 21 2 18 7 24 0 19 8 21 8	20 9 20 2 23 4 14 5 20 2 20 2 20 2	25. 5 22. 0 20. 2 21. 3 20. 9 22. 7 4. 45 1. 45	22 6 23 2 20 7 21 8 21 1 23 2 22 70 1 70	22 3 23 4 21 6 22 4 21 7 44 6	20 0
FEED (	191 192 193 194 195 196 197 198 199 200 AVC 5 D	20 23 16 17 21 16 16 17 21	7 3 3 0 7 0 7 0 7 0	21 7 24.0 17.2 20.2 21.2 19.7 24.0 19.8 21.8 21.15 2.07	20 2 20 2 20 2 20 2 20 2 20 2 20 2	25. 5  22. 0  23. 7  20. 2  21. 3  20. 9  22. 7  21. 45  1. 65	22 6 23 2 20 7 21 B 21 1 23 2 22 70 1 70 (DB) 5 !	22 3 23 4 21 6 22 4 21 7 22 6 23 11 1 70 3 MHDL/KG DAY 34	20 0 20 0 22 6 13 6
FEED	191 192 193 194 195 196 197 198 199 200 AV3 S D	20 23 14 17 21 16 16 16 17 21 18 2	7 3 3 0 7 0 7 0 0 7 0 63	21 7 24.0 17 2 20 2 22 2 18 7 24 0 18 8 21 8 21.18 20 7	20 5 20 5 20 2 20 2 20 2 20 2 20 2	25. 5  22. 0  23. 7  20. 2  21. 3  20. 9  22. 7  21. 45  1. 65	22 6 23 2 20 7 21 8 21 1 23 2 22 70 1 70 (DB) \$ !	22 3 83 9 21 6 32 4 21 7 44 8 23 11 1.70 3 MiDL/KG DAY 34	20 0 20 0 20 0 22 6 22 1
FEED	191 192 193 194 195 196 197 198 199 200 AVC 5 D	20 23 16 17 21 16 16 17 21 18 2	7 3 3 0 7 0 7 0 0 7 63	21 7 24.0 17.2 20.2 20.2 18.7 24.0 18.8 21.18 21.18 20.7	20 5 20 7 20 2 20 2 20 2 20 2 20 3 20 2	25. 5  22. 0  23. 7  20. 2  21. 3  20. 9  22. 7  2. 45  3. 65	22 6 43.2 20 7 61.8 21.1 23.2 62.70 1.70  C(DB) 5:  DAY 27	22 3 23 4 21 6 22 4 21 7 22 6 23 11 1 70 3 MHDL/KG DAY 34	20 0 20 0 22 6 13 6
	191 192 193 194 195 196 197 198 199 200 AVG 5 D	20 23 16 17 21 16 16 17 21 18 2 100 19 21	7 3 3 0 7 0 7 0 7 0 63	21 7 24.0 17 2 20 2 22 2 18 7 24 0 18 8 21 8 21.18 20 7	20 5 20 5 20 2 20 2 20 2 20 2 20 2	29. 5  22. 0  20. 2  21. 3  20. 9  22. 7  2. 45  3. 65	22 6 20 7 20 7 21 8 21 1 23 2 22 70 1 70 20 5 9 24 4	22 3 3 3 4 21 6 22 4 21 7 22 6 2 3 11 1.70 2 4 2 3 4 2 3 3 2 3 2 3 7 2 4 4	23 0 27 0 27 0 22 6 23 1 1.6
	191 192 193 194 195 196 197 198 199 200 AVC 5 D	20 23 16 17 21 16 16 17 21 18 2	7 3 3 0 7 0 7 0 0 7 0 7 0 7	21 7 24.0 17.2 20 2 22 2 18 7 24 0 19 8 21 8 21.18 2 07 7 74VLENE GI DAY 6	20 5 20 2 20 2 20 2 20 2 20 2 20 3 4 56	25. 5  22. 0  20. 2  21. 3  20. 9  24. 7  24. 1  25. 7	22 6 23 2 20 7 21 8 21 1 23 2 22 70 1 70 20 (DB) 5 1 23 0 23 1 20 6 24 4 22 7	22 3 21 6 22 4 21 7 22 6 23 11 1 70 3 MHDL/KG DAY 34 23 3 23 4 23 3	23 6 23 6 23 6 23 6 23 6 23 6 23 6 23 6
FEED (	191 192 193 194 195 196 197 198 199 200 AVS S. D CURSUMPT RAT 201 202 203 204 205 207	20 23 14 17 21 16 16 16 17 21 18 2 7000 19 21 21 21 22 22	7 3 3 0 7 0 7 0 63	21 7 24.0 17.2 20.2 21.2 19.7 24.0 18.8 21.18 21.18 20.7 7 74.4 0 18.8 21.19 2.07	20 5 20 5 20 2 20 2 20 2 20 2 20 2 20 2	25. 5  22. 0  20. 2  21. 3  20. 9  22. 7  21. 45  1. 65	22 6 43 4 20 7 41 B 21 1 23 2 22 70 1 70 23 0 23 1 20 6 24 4 22 9 23 5	22 3 23 4 21 6 22 4 21 7 22 6 23 11 1 70 3 MHIDL/KG DAY 34 23 3 23 3 23 3 24 4 27 22 4	23 0 27 0 27 0 22 6 23 1 1.6
	191 192 193 194 195 196 197 198 199 200 AVC S. D CONSUMPT RAT 201 202 203 204 205	20 23 16 17 21 16 16 16 27 21 18 2 700 19 21	7 3 3 0 7 0 7 0 63	21 7 24.0 17.2 20 2 22 2 18 7 24 0 19 8 21 8 21.18 2 07 7 74VLENE GI DAY 6	20 5 20 2 20 2 20 2 20 2 20 2 20 3 4 56	25. 5  22. 0  20. 2  21. 3  20. 9  24. 7  24. 1  25. 7	22 6 23 2 20 7 21 8 21 1 23 2 22 70 1 70 20 (DB) 5 1 23 0 23 1 20 6 24 4 22 7	22 3 21 6 22 4 21 7 22 6 23 11 1 70 3 MHDL/KG DAY 34 23 3 23 4 23 3	20 0 20 0 20 0 22 6 23 3 24 41 23 6 23 3 24 4 27 7 27 7

<sup>\*</sup>Statistically significant from controls p ≤0.05 ····

Table 3 (cont.). Feed Consumption (g/rat/day)

		Marie Communication of the Com	<del></del>				<u> </u>
grindring grown . General section of property of the forest sections and section of the section							\$ c.
FEED CONSUMP	rion		CONTROL	5		d'a	
RAT	DAY 3	DAY 6	DAY 13	D& Y 20	DAY 27	DAY 34	DAY 41
271	20.7	22 0	17 13	19.4	30 6	21 4	<b>3</b> 5 1
272 473	21.3	23 2 18 8	21 2	21.9	25. B 22. 4	23 2	23.7
273 274	18 0 24 0	25.2	E4 &	81.7	<u> </u>		<del>- 24.</del> 7
275	21 3	50 O	20 6	50 0	50 3	20 4	20 5
276 277	22 3	22 3	27 9	22 5 24 0	53 5 53 A	23 2	20 4 20 4
2// 2/5	Z1.3	- 21 3	210	<u> </u>	2	**************************************	278
279	24.7	25.2	27.1	27.1	27 6	27. 9	28 1
250	22.0	518	2 · 7	* Z B	83 1	2.1	#3 7
AVC	£1.43	66 66	EE 02	62 76	23 83	27 67	24 07
S D	1. 93	\$ 05	2 73	2 36	2.26	2.20	2 14
		gan manususinga ususininga a seriangan hannan na serianga					
400-material adjustment and a second			construction (APA) - Commerce occurrence (APA)				
hanning-row-14-managaran managaran ang sang arawa ang	AND THE PROPERTY OF THE PROPER			On the second			
отобитурного под браничения в предостивного объекто объекто от отключения в под от отключения в под от отключения в под от	emmercipality and embargas emanages emanages	e outside to the transport of the second of	obs Child Colonia Children Colonia Colonia Colonia Colonia Colonia Children Colonia Colonia Children Chil	eriken-eremonali baserana veno e anveramono canacam <u>ana b</u> aryana	**************************************		SNASSOCIONES CONTRA CONTRACTOR CO
n Constitution and the constitution of the second s	Manner - inquistrative remarks or the contract of the contract	WALLES THE STREET STREET	and the state of t	entergraphics	College Colleg		SAME OF THE PROPERTY OF THE PR
	· Constitution and a second						
on definitions in profession to the real entire and entire and entire profession profession from the residence	CONTROL CONTRO	near-rengementalgogical-entitiples control time control			ня Война со под на объем на применя на прим	A The Control of the	**************************************
Total and the second						We was a state of the state of	Name of the Control o
a-vindelileren katuryandalilijättya, attitutumaastela kasiliitätiön sannastelilää senistattuttataastel				performances (SCO) - session transcriptions - defe-	constructive draginal fill in model in the property construction of Tables and Construction (Construction Const	Control of the Contro	
militari variatiisi vaasitiikki. Ciispooliidii mirjoona nooyaliyydeyddigaaddigaaddigaaddigaaddigaaddigaaddigaa		****			varanno distributa sustano di Carino	20/2/2/22	
elementarium prominintelibilitarium inteligium underprometation under materiale (110 peta principamente) metr			interview of the state of the s		de malliment del l'important de marchite con l'important de malliment de mal	m - 44 d. Sirver control of the second	
						3375-754 City Avenue 38690 Avenue 38690	
	and the second s		witer West (1986) with the state of the stat	Montal William Language Control Contro		over a contract of the contrac	
	The Tampatan are done as a succession of			70 AND 12 AND 17 AND 18			
				•	*		
	philippe with the second secon	tive officialism systems are entireplacement in the other entire law.	- water desired the second	n State (State Control of the Contro	and the same of th	y o - 11 - 12 - 12 - 12 - 12 - 12 - 12 -	
				e			***************************************
	Carrio Carrio (Carrio) (Carrio) do de la compresa de mission de compagnatura de						
en de la companya de							
	i Para y Talana Cala (Calana) da da a comunida para professio de Calana (Calana) da Calana (Calana) da Calana Para para para para para para para para	r-Village, weighter warmstein der der zerführt vorließe gelöstigt gelöstigt geleiche geläßigt.	;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;	de de la company de la comp	The same of the sa		
		- Palling angles annother the confidence of the palling of the pal					The distance of the second

	5		00	0	0.0				C		0	0 6	0	C		000			2	0	0	0	<b>)</b> 0	٥	٥	0	0		0	- Constitution of the contract	*Negacijuscommenterosommenterosom	
		•	00	0	000			7.603	•	0	0	D C	0	6	0	0.0	STATE OF THE PROPERTY OF THE P			0	0	0	<b>)</b>	0		0	0	0	0	posteonica constitutiva disenta di persona di	Simple and an additional appropriate property of the same and same	
		•	40 C		n 4				*	E.	A	೧ €	S Commence	N	n	2.3	Andreas de la companya de la company			n	¢	A Terroscontinum of the second	<b>0</b> 4	0	। इच्छी	0		U,	e. G	Acompression places of the contract of the con	mingeres edita este estatutata accidentación (editación (editación) este este estatutación (editación) este es	
and the second s	8	*	00	0	9 C			Š	c	0		* 6	0	0	enti	0.8	and the second s	SECTION CONTRACTOR CON	S	N	0	0	- F	O	ent	=	0	<b>*</b>	000	Martine of the control of the contro	CONTRACTOR OF THE PROPERTY OF	
e en total de la company d	ZOMA	85	20	98	74°.			****	C	3.6		, @	82	98	7 80	70.0			Impa	*	76	Eb.	) f	9 6	*	ව්ර	60		0.0	e to the contraction of the cont	and the second of the second o	
BMSZSA1999AA ITOJOOJSIA yeevee yo yo go go go go go	POLY	S	£ =	77	17.3			2 5 5	***	8		C 4	16	2	ea	19. 3	ALGORISTICS AND	Andrewski skieder de deutsche	Š	CV	0.3	Section of the sectio	0 1	9	474E	*	2 &		7. 6	ANIMATANA II-IIAANIAAAAAA III AAAAAAAAA III AAAAAAAAA	and the second s	
	JWC		875	9700	1766.7			J	565	10700	11700		0069	8700	11500	10950.0	AND MAIN AND AND AND AND AND AND AND AND AND AN	3 M/10/M/6	288	0021	14000	9400	0048	15400	13700	1 < 6.00	10000	1677 8	2(36, 7	APTELISTICATION PROPERTIES CONTRACTOR CONTRA	Mende destruction of 100 of males of 5 feet and and 500 of the second of 500 of	
1001 22 MG	W. 26.	72 72 73	200		26.00			×	n C		26.2	7) (0 ) (1) (2)	30.3	â		20 73 ¢		en'	25.24	8	29.8	30.4	3 C	32.2	9.	7.5	31. 4		0 88	* A C C C	5,01	
	William B. M. Transmission	S	<b>3</b> 32	19.7	20.02 20.03	2000	FINCH COM	Ž	Sa es	i .	NI	7 C			F8	20.00		ETHER (DB)	HJM	-0	- 1 m		D &		2	7. 2	. 8		0.02		- C** V * C + 23	
W. D. BULLA	T. T. T.		e C		77.60*			2	87	63.3		r C	36.2	. 3	5.	61.12			. A.784	. 0	27.4	7.1 6	e f	\$ 1.5E	6		8	47. 82	7			
4		\$		6.87	6.393*				40	7.96	7.83	) a	6.94	2.47	7.57	186.6			268	*	60.00			01 6	8	000		r: *	693 0			On the second se
			8°	\$6	0 4			7	(\$ <sup>6</sup>	25	or on	? ?	ĥ	. A. A. Commenter	0	86.8				*			· **	6.8	\$ <b>4</b>	*		< ***	e a			A TOTAL CONTRACTOR CON
KAROORINAAN PROGRAMMATA KAROORINA KA		910		20.0	12.76°		۰		e e	44.0	Married Marrie	, C.	11. 9	13.8	U.	* 2 ° ° °	#b				w :			18.3	C 48				6		\$	COLORO ANTONO PROPERTY PROPERTY AND ANTONO PRO
**************************************	Š	Į.	m g		288				è	192	192			2.22	\$	8			Š	K	2		ŝ	2				Service Control of the Control of th				

Table 4 (cont.). Hematology

	SPECIAL CONTRACTOR CON												
					gardagadasadaga carrosidos estimanos hodos especientes.		MACCOLO LE COMPANY MACCOLO POR CONTRACTOR DE COMPANY DE	THE CONTRACTION OF THE PROPERTY OF THE PROPERT	menten en e	• 1959-00/1998-rates contract	0		
		2	.38.36	2		MC LAT	348	PMX	PW2H	EDG			
	THE PROPERTY OF THE PROPERTY O		1	****	4	P		c	Œ.	0	C.		8
THE CONTRACTOR STATEMENT	73.0	7		" " " " " " " " " " " " " " " " " " "	17.8	31.3	11500	B	79	0	n	01	0 (
272	* (	Ø 4	) = 0	, i	12.5	0.50	7500	And I was a second	88	O.		e c	- E
			9 40	13 8.5	5.	ក	0000	≈ §	7 6		7 67	9	) G
		SOURCE CO.		managed Land American	17.8		700501	10	90	0	0	0	0
A 7 &	13.7	(C) (S)	0,0	- r 3 r		, C	B700	6	78			Q	c
energias y syrigh executives consistent energial executives and the construction of th		22	68.8	5.5. 1	١.	() ()	9400	6	Î	6	8	C	
8/K	. 0	. 6	B 45	of the Reserven	12.6			01	77			0	0
280	2.5	0	er. Ti	21 2	17.5	*	20.00	= [(			Eo Co	S	0 0
	18,88	25.9	8.771	SF	16. 97	2 . C	0.000	o E		5. a	7 2 2	o d	2.0
		ğ	MINISTERIOR CONTRACTOR	And a second									
		And the second s		THE THE CONTRACT OF THE PROPERTY OF THE PARTY OF THE PART	population proportion and the proportion of the	THE THE PROPERTY OF THE PARTY O	PROPERTY OF THE PROPERTY OF TH						
•			THE PARTY OF THE PROPERTY OF THE PARTY OF TH	Approxy acom acompanist excerppe with except that we have	AND THE PERSON NAMED AND THE P	NAMES OF THE PROPERTY OF THE P	ALIEN ANN AND EXPERIENCE OF THE SECTION AND AND AND AND AND AND AND AND AND AN	ASSESSMENT OF THE PROPERTY OF				sector and a section of the section	and and a second
<u>Linguistica de la companya de la co</u>					DO DO COM	THE COMMENT OF THE PROPERTY OF	THE PROPERTY OF THE PROPERTY O		Newscander Charles and Control of the Control of th				ne netera i netera i interes con composita por proposita con consecutivo de conse
appionsesses (Alectronical management of the Company of the Compan	watering in the customer of the continue of th	Monte on contains of the conta											
			Approximental surprise of the	Que esses esses especiales (S) higher free particular de la company (S) especiales (S) especiale		and of the second secon		THE PROPERTY OF THE PROPERTY O					
				TO CONTRACT THE PROPERTY OF TH	namente de la company de la co	MALOGRAPHICAL PROPERTY OF THE	AATA CAA CHICKEEDOO OO	- SANA CONTRACTOR OF THE PROPERTY OF THE PROPE	Allege in Section Constitution of the Section of th	a contraction of the contraction	etermental interpretations of the second		
Millioning property property and contract the contract of the	odoccomostacciente, interpresentamente de constitución de cons						•	Company of the Compan	NEEDEROOMERS (NA PROPRIESTO CONTRACTOR CONTR		No. of the second secon		Annalum cas rock (CAMISA Is) ryc. op crat cost (Annalum Castella Is)
	***************************************	STEEL ST	CONTRACTOR DESCRIPTION OF THE PROPERTY OF THE	<u>uninianisticinanisticina en </u>	STREET THE PROPERTY OF THE PRO	USS SOSTORISM AND ANA ARCHITECTURE STATE OF THE STATE OF	The section of the se						
	,		NACO CONTRACTOR CONTRA	And the second s	ANSWERSON STOLEGISTISTISTISTISTISTISTISTISTISTISTISTISTI	SCHOOLS CONTRACTOR AND	MEDISCONICIONALIA PROPRIO DE PORTO DE P	Andrew Conference Commence of the Conference of	<u>VORMODOS SIGNAS OR ANTONIOS CONTRACTOR CONTRACTOR SIGNAS CONTRACTOR CONTRACT</u>	elopposusciasus III (lication establish			
			100000000000000000000000000000000000000		Heropherstandingsrepresentations of the second general second general second general second general second gene	тун-Аттиран-Оффакамшаашбатте 25кт нгод т	and the second s	CERTIFICATION CONTRACTOR (ACCIDITIONS FOLIAMETERS)	COLUMN TO THE PROPERTY OF THE				
AN GOGGOGG STALLANDER STALLANDER STALLANDER STALLANDER STALLANDER STALLANDER STALLANDER STALLANDER STALLANDER S							Department of the second of th	<u> 10 juga nes 021 0000 filosopidopo sibreta dia 00000.</u>		THE STREET PROPERTY OF CONTRACT PROPERTY OF THE STREET, THE STREET	Andrews of the Company of the Compan		
		Megapanan programmen and management described and describe	SALLIAN AND SALLIAN STANDARD SALLIAN S					447					
				near procession and the second desirement of the second second second second second second second second second		saniani kriptoi reesii ilee kiristaa saasaa saasaa kiristoi ok					,co		
A CONTRACTOR OF THE PROPERTY O	Vasas kais saasat kansaa kala saat ka	entres necessites contributes (fine)		special production of the second seco	Service Control of the Control of th	graceromoranes-s-s-passacranesacranes	ORGANISTICAL AND ALL A	moderno consequence of the second sec	osopysm viscotoriakomonikomonikomonikomonikomonikomonikomonikomonikomonikomonikomonikomonikomonikomonikomoniko				
					(Annalysis and an annalysis and annalysis and an annalysis and annalysis and annalysis and annalysis and annalysis and annalysis and annalysi	enement of coopsissions and an extension of the coopsission of the coopsis of the coopsission of the coopsission of the coopsission of the coopsis	sdrs-l-sp-Lol/GDAGGSQQQAAGGSGTATATATATATATATA	STREET TO THE PROPERTY OF THE	A 1990 COLUMN CONTRACTOR DE CO			on and the control of	
			Đ			TO COLO DE LA COLO DE	ROOMETPREFEROMER CONTROL AND THE TOTAL PROPERTY OF THE PROPERT	разына денения принципальный в	noszonán megandán (Alaka Persa) formáltatón a szon este	ANTONIO PEROPERANTA METATORIA		8	
							ges 104,2 (\$100,000 OCCOPOCIO FCPrior) minus meneral difensalem	<u>dentalise curses es displatatique de constitution de secuencia de constitution d</u>	монгонизаци тепропроводом да на дажна техните	appopopusatistosastasastasastas		9	O PERCONAL PROPERTY OF THE PRO
		DEREGGERAN PROPORTIONAL VINCENCIA DE PROPORTION DE LA CONTRACTION DEL CONTRACTION DE LA CONTRACTION DE	ALGORISMA MANAGORISMA CONTRACTOR	appacking prevent for the frequency flowing the following				да параж почеден жизным край болатына төмөм	magoray na aj seksikilisilisilisista Grazza teksimisi ni da seksini ini ini	anamamageoccogny docknownskip. Effeth	saperipoint disconneces and places of the contract of the cont	t .	
		Statement Assertation of Statement S	NAMES OF THE PROPERTY OF THE P	<u> 1980/fringeriorania de la compositor d</u>	etysak danadalibakitalibakitalibakitalibakitalibakitalibakitalibakitalibakitalibakitalibakitalibakitalibakital	THE STATE OF THE S							
					DATE OF THE PARTY	CONTRACTOR OF THE PROPERTY OF	111(00)00/14/1100-0-11-10-10-10/1////QL-013100000	Additional and produce and pro	an a la conscionación de la composito de com				
	Annual Company of the			Princi ETTE 945 EN BARROLIO ARRANDA SA	provingsamawaadiri///XXXXXXXQXQQQXXXXXXXXXXXX	n - (d. (dis - val) (d. ol) pjedod Sill Siljinda primapekje	amination designation memory and bloom is challenge associated	gegg en jung jepan kanar v Oct. (KNP president) VIII-r in in	egenderiktististististä SAM-reddikkylypedanike-op///pik/13/SECO-redd	10000114000199944	OUTSTAND PROPERTY OF THE PROPE	e de la company de la comp	CONTRACTOR OF THE PROPERTY OF
					2/77/2/00000000000000000000000000000000	constitution of the second	Constitution in the Constitution of the Consti	game de des présentes de la Compute de La computé de la Compute de La Co	um-appoint (disul-statementary)-tight-object-bissisisisisisis	Apidagosobini Neppina iyo dilikida oo	er-Application etocococococococococococococococococococ	THE THE PASSE OF T	announterioristationistationistationistationistationistationistationistationistationistationistationistationis
			New ORDER CONTROL OF THE CONTROL OF	уминиционального применения в п	174				engagen glob filiphia sembra sembala de esperado de esperado de esperado de esperado de esperado de esperado d	AND THE REPORT OF THE PROPERTY	POTENTIAL STATES OF THE STATES	esterocomo (A emermente acresamente (1990) a del del del	THE PROPERTY OF THE PROPERTY O
	Printerson Contraction of the Co	400000 NASAKOTI SA-SANSAN KANAN KANA		gyjakogajasikanan manakan vanan adamaterateraterateraterateraterateraterater	Major Commission (Commission Commission Comm					A CONTRACTOR OF THE CONTRACTOR	PHASE CONTRACTOR OF THE PROPERTY OF THE PROPER	DECEMBER OF THE PROPERTY OF TH	AND CONTRACTOR OF THE PROPERTY
	(A) The second s		parameter de la company de la	NONESCONMOSCOMISSISSISSISSISSISSISSISSISSISSISSISSISS	400 and the contraction of the c	s el est comme a proposition de la constitución de	me (c) commonwell possessionally	Epiperacija objekto i jeda izali izali provinstava i jeda izali izali izali izali izali izali izali izali izali	e og en er de de la	No. Anti-contraction of the Contraction of the Cont	-		CONTRACTOR
									BEFORE COMPANY TO SEE STATE OF THE PROPERTY AND THE PROPE	granden de company de de la company de de la company de la	erio esconado de composições de comp	assus necessitatististististististististististististist	

Table 5. Clinical Chemistries

CLINICAL	HEMISTRY	DIEI	HALENE OLA	COL MONOS	II YLLEIHERL!			
	2.2.2.2	07	<u> </u>		LK PHOS		22.22	CREATININE
193		48	36		244			0.55
18:	3	85	29	424	184 278	19 17	\$5 97	0.30
18°	demonstration of the second	<u> 45</u> 75	37	601	871	8.3	128	0.50
A		8 3	32 7	652 5	219.3	14.8	<b>₹8</b> 5	0 512
		4.2	And the second second	7771	<u> </u>	<u> </u>	20_ <u>å</u>	0 07:5
CUTNICAL	HEMISIRY	DIEI	HALENE ELA	COL MANAGE	UTYL STHER		MULZKC.	
P.A.		<u> </u>	EGPT		ALK PHOS	RUK	QLUC	
	•	73	23	719	78		eteroreste gradit	
19	der and the second seco	80	35	367	162	26	92	0 80 0 80
. 17	510 <del>1</del>	<u> 55</u>		71.9	245			
19		68	30	418	108	10	92	and the second second
10		75		472	257	12	46	O 40
19		71	20	8,55		4 9	101	
50		91	37	314	193		107	0 50
ALL DESCRIPTION OF THE PROPERTY OF THE PROPERT	ve ?	78 1	30 1	493.9	187.7	12 1	110 1*	0 45)
and the second s		9 2		1517		22		<u> </u>
PI TAIT CAT	CHEMISTR	v DIC	INTERIO CO	Y-01 Y0 11	UTYL ETHER		MUDL/KG	
12/		GDT	rapt	I C.H.	ALV PHOS			CREATINI
	and the second second			es proje frant	309	9.3	144	0.90
2.		<u> </u>	28	and the second s	190	14	102	0.60
30	r 1981	116 77	57	514_	149		121	0.50
2(		65	23	2:29	163	16 14	127	0.60 0.35
20	٠	_84			141	13	107	0.50
29		75	13	312	125		124	0_50
- Commonwealth Common C	) <u>@</u>	<u>. 67</u>	20	455	190	13	175	0.50
	)	_65	57	472				
Market and Commission			a- a- 200		1924		132.4	2.500
	A!/Q	77.5	2 <u>5_2</u> 7. 4	150.2	31.2	1.0	23. &	0 044
	. \$ .	13.7	/. s	NAMES OF THE PROPERTY OF THE P				
							The second second second	A STATE OF THE PROPERTY OF THE

Table 5 (cont.). Clinical Chemistries

						**************************************	
		8			1		
CLINICAL CHEM	ISTRY		<u>coursous</u>				m m m - 500 00 a 10 a 10
	ecor	5697		LV P405		20118	<u> </u>
<u> </u>		*			10	132	0.50
271	. 24	32	503	164	12	148	0.55
272	. 93	23	272 1002	129	11	121	
223	21	32	302	190	11	144	0 50 0 60
274	65 71	28	274	221		133	0.60
276	• 100	23	1152	248	15	172	0.50
277			365 <u>30</u> 4	20¢	10	140	Q. 50
278	<b>63</b>	18	897	145	11	132	0.50
280	61	17	350	151	•	166	manifest by the company of the compa
	80 2	26 9	549 8	177.3	11.3	141.8	0 575
AVO S.D.	15.0		253.5			and the second s	
Designation of the last of the	The second secon						
Wheneight experies to again the part of th							
					occupation and the second seco	Section of the sectio	Control Life, Quarter and the second control of the
	MINISTRACTION OF THE PROPERTY						
02200001444							and the second s
			NOONIGOROUS CONTRACTOR	and the second s	CONTRACTOR OF THE PROPERTY OF	The state of the s	
Control Research							
							and the second
			NATIONAL PROPERTY OF THE PROPE	Control of the Contro	Note that the same of the same		
divinita tura entra di Contra di Con			Access to the second se	orași de la companie			
SAME IN THE RESERVE OF THE PARTY OF THE PART				and the second			establine de Caracia d
•							1974 Marie Charles Charles Charles and the State Charles and the Charles and t
				невобору в при в при В при в п		2000/442((((((((((((((((((((((((((((((((	
	annann (Allemani (Al Allemani (Allemani (Allem			enterfolgen verschiede verschiede verschiede verschiede verschiede verschiede verschiede verschiede verschiede Verschiede verschiede verschiede verschiede verschiede verschiede verschiede verschiede verschiede verschiede			

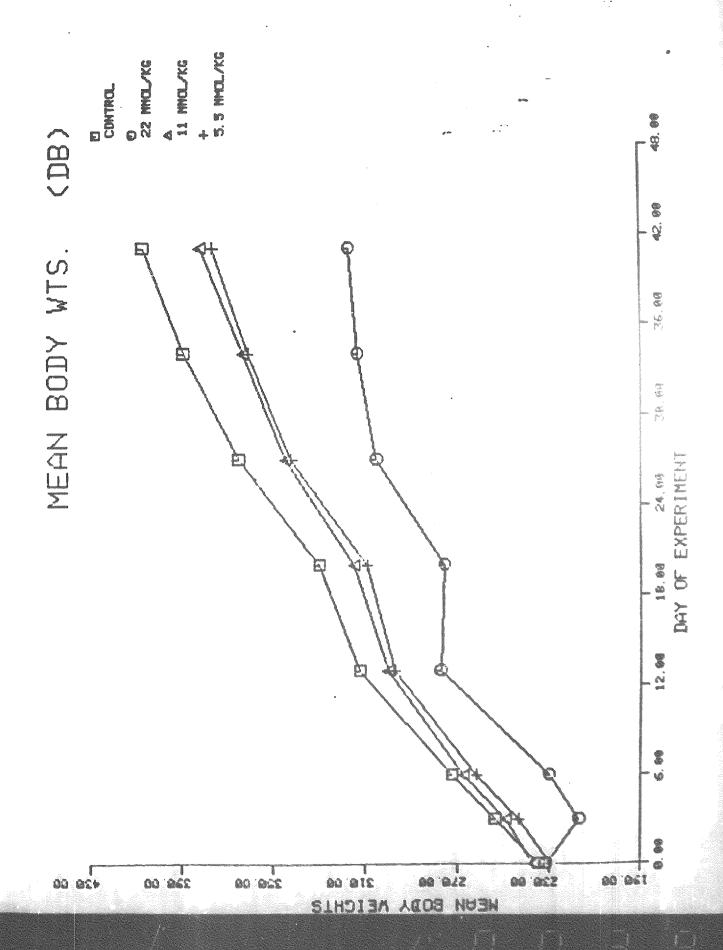
	- CO.
	A 100
ů	-
	PASSACREPANDE DE PROPERTIE PARTICIPANT DE PROP

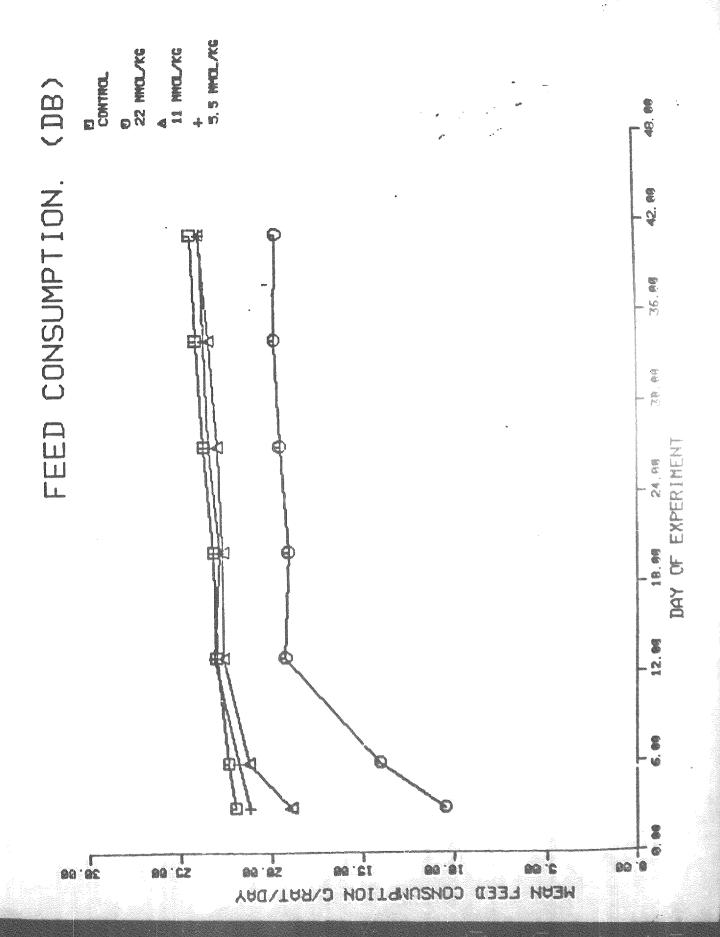
													A COLUMN TO SERVICE STATE OF THE SERVICE STATE OF T
			7		¥		e e	1	8		i.	200 a 100 a 100 a	•
3 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1	STATE OF THE PARTY						30.0		S	7.05 1.05	3	1.24	
	Ž.		i C	eser Laser		0 43	8.70	2.62	8	1.78	0.60	8.	9. 22
	THE RESIDENCE OF THE PERSONS ASSESSMENT ASSESSMENT ASSESSMENT ASSESSMENT ASSESSMENT ASSESSMENT ASSESSMENT ASSESSMENT ASSES		24		7.0	29 cg 1 11			7 P	<b>&gt;</b> (	> 1 5 6	0 °	\$ i
	Š		**	7.9	. 8	0.90	0.0		0.42	1.41	0.03	50.7	8.8
A CONTRACTOR OF THE PARTY OF TH			* 495	0 4		6	0.3170	n	0.9738	1.830	6.670	1.272	
					6	8	20.0		0.061	0.12%	0.027	201.0	707.0
								Pagger code (by ready, speciment constituted an extension of the speciment code (by the spe		anter stolen ett state stolen ett			
		VETMLERE ALTON				paperal Septemb							
		M 63/17	<b>X</b>		*	MENT WITH	W.	RESIES MI	3	SHATE OF	7		
						8			94.0	1.77	3.0	5	0.37
und yest		6.0	ri e				: £	9 6	0 80	20.0	0.00	100	0.27
6			1 1 2	5				3.72	0 a0	2.02	0.57	0.60	77.0
		33	1 2	0		- 1		2.93	0.79	A. 03	0.00	8	). 7&
9			3.42			8		D (	0 f		9 4	) C	
		28.01	14 5			7 70		3.12	25.5			0.02	2.12
		11.75	ភព	3 c	်င် ဝင်		0 0	n n	0		3	0.0	0.27
	. 22 % .									. 25	3	, 45.9°,	9276
					0.033	260.9	9292	0.192	180.0	0.104	0.03V	0.143	0.05%
								o)nggggssmappuppuppupcka-a-a-jöjdfillokt					
								AND THE PROPERTY OF THE PROPER					
		DEFINER CYCL NAUEV				) 3.3 mac/A0	25/80						**************************************
			×	M VSV/IIV	A No.		o p	TESTES EL	×			MEEN W	pæ
									184 0		0.2.0	0.75	0.21
		S &	`	*	- C	18		2	0.93	7.65	0.35	0.42	0.03
		9.50	2.03	:: 13	0.72	0.91	16.0	2.66		87 e	0 c	) C	) C
		10.01	00.0	25.07	0.00	1. 1 3 3 mm		3. 20 1. 20 1. 20	9 C C C C C C C C C C C C C C C C C C C	0.5	200	V6 9	0.17
		10.73			0 6			2 6 5 C		88	0	0.72	00
				0.,	0.53	1 48		3.19	0.82	2.13	0.32	2.70	20
					25			000		. ao	0.00		V. 56 8
		. ĝ.	2.5		0.63	§ .	C. 33	9.3	0.97		8 0		· •
					280		0.344	3.074	O. CHIE	N S S	0.030 0.030		) (0 (0 (0
			8				TO E TO VIEW	(CONTROL		oscingstonecy-vision-in-on-therassegradiffibility			
		ě			707.P518.5	70°02	AND COLOR OF STREET, N. CONTRACTOR OF STREET,	edisseption of the control of the co	www.docoman.com.com.com.com.com.com.com.com.com.com	ensissamana designamana desistativa Vidanzana			
		986	53 5 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	A B "CONTRACTOR AND THE CONTRACTOR AND THE CONTRACT	1	Management Approximations	STATE OF THE PROPERTY OF THE P	onitaman nasomos Nyonae (2) Arey e e Aperte e notamente e se 4	CONTROL OF THE CONTRO	annua energenesississississississississississississis		Announce to the control of the contr	

					Sold free contract of the cont	allonoscopalistico contratos establistica en el		nessimmenten resumenteles most les institutes es	observed and a second a second and a second	sentenden der Amerika sektidan stemstetet 1800 til se				
				Y A V W	***************************************		S.	TESTES H	e casarina de servicio de la casarina de servicio de servicio de la casarina dela casarina de la casarina	BRAIN	**************************************	W WALLEN WY		ŀ
K		72.01		67 6	0.77	101	6. 38 EE	6.0	0.65	\$ . n	50.00	27.0	8:	l
2/2	253	9. 90	2.60	S:	0 78	-#	0.31	3.19	0. 00	2.02	0.97	0.66	0 0	600000000000000000000000000000000000000
) <b>%</b>	S.		2.93	.: m	0.73	2.3%	8	2.93	0.77	1.96	0.91	0.84	22 23	
27.2 27.2	0.5	7. 66 9 FA	6 S	- 14 15 16 16 16	4 5 0 0			1 6 13 5 13 5	0.00		0.0		<u>.</u>	
	347.	10.25	G	- 6.5	0.00	1.00	0.30	0 s	0.05	1.04 40.1	0.00	98.0	2:00	
278	386.			21.10	0 0	1.55	200	2.37	0.78	2.79	96.9	6.32		
	77	10.73	10	0,7	0.77	2	9.30	2 6	0.84	2.13	0.97	0.61	91 :0	
	377.0	10.387		C.	0.750	 8 	0.303	u. 073	0.020	88	6.033	0.673	2 6	•
		1.292	0.173	0 418	0.063	0.152	0.019	0. 167	90°0°0	0.094	0.0		0.023	
CATABLE CONTROL CONTRO		<u>gasanamenonproceptiganishin merancaha</u>			strongen datestro Opini il providente approprieda	on de la company de la comp	STANDARD CONTRACTOR STANDARD CONTRACTOR	assassanda a seria a sasassana a seria a sasassana a seria da						
		TO THE PROPERTY OF THE PROPERT	production summer brains and continues of the continues o			allocity an part of a transfer and transfer	948-464035 ST-01041001100000000000000000000000000000	rgautoma, residensial basterenter representation discossibility de	Olomonturditurio e secolulisti di di Colombia	New Activities of the Activities de Sandal Conference (Conference) (Conference)			Mary Construction of the C	
MERCHANISAN CONTRACTOR	and and the second seco				COLONIA SE	Programme and the second secon		er frådstekkenskyrskelskelskelskelskelskelskelskelskelskel			enter entre de la companya della companya della companya della companya de la companya de la companya della com			
									enne quantizatatatatatatatatatatatatatatatatatata	ner recommission that the commission of the comm	encellocapterist (december female	A STATE OF THE STA		
									CIVIC DAY WAS A STATE OF THE ST					Operations
rateges des des formations des constructions parameter and parameter and parameter and parameter designations.	APPROXIMATION CONTRACTOR OF THE CONTRACTOR OF TH	international province of the		on and a communication of Laboration of Communication of						6				
THE STATE OF THE S	*	Secretarion or procurate description of the Secretarion of the Secreta	Month of the Control	Viginistic de la company de la	CONTRACTOR AND	managata kanganga kanganga kangangan kangangan kangangan kangangan kangangan kangangan kangangan kangangan kan	positos econocididos de participados de la propesa de la p			any and opposite transcours of transcours of transcours of transcours of transcours of transcours of transcours				
		**************************************						000000000000000000000000000000000000000						]
						N. P. C.						*		
					cognus actification (Elektronomich racoombination	and billion construction and an analysis of the construction of th	encontraction and property of the contraction and the contraction	and the speciment of the state						
				neessaatiselteelteelteelteelteelteelteelteelteelt	de de la companya de		Andreas de la company de la co							
	Security of the second security of the second secon	a a contraction of the contracti	siemistiioomistiiselliselliselliselliselliselliselli	<u>erentativastikon (of poesitormus (retterior</u>	ohis sautoinas d'edifina jouroitoin aconantilo	A SECTION OF THE PROPERTY OF T			arantesoromoonapsilitajakohttonoo	and de constant of the second	¢			
		· STATES AND		SCHOOL SECTION	n-cuuntetenssielelelelelelelessessesses		New OF PROCESS ASSESSMENT AND ADDRESS ASSESSMENT ASSESSM	20000000000000000000000000000000000000			900000000000000000000000000000000000000	ATTOCOMICS CONTROL CON		
										•		- 6		
		SOUTH STATE OF THE	Matthetassiantenedassiantentenedassiantenedassiantenedassi	<b>4/</b> 000mmeterse0000000000000000000000000000000000	0000 productive State (Control of Control of	angalonanykanoan-kannanananykokokokokokokokokokokokokokokokokokoko	occupation also proclimate research and the control of the control	AND THE PROPERTY OF THE PROPER				* **		•
		(CANA)		AND WEDPERSONAL SERVICE STATES	anstresonder annimieration and and and and and and and and and an	ENVEYOR - 11 - BANGARANNO ACTUARINA TO THE CONTRACTOR OF THE CONTR	genoropianen (Oriotheleako) yoldulu tut	populari un contrata de constato y s'essencia de la constato de la constato de la constato de la constato de l	actions and the contract of th	AND THE PROPERTY OF THE PROPER				
		MONTH PROPERTY OF THE PROPERTY	Commission of the commission o	NOTE TO SECURITION OF THE PARTY		aterinos/montejosesporarentesporarentesporarentesporarentesporarentesporarentesporarentesporarentesporarentespo	operation of the state of the s	Missianie (in the company of the com		ongsommunational individual decomposition (Application (A		*		
	1977 to the second seco	with the second			nuvorintensialentenstatutogistatutogistatutogist	emmerselindensenjöttepermenensetsistenselintelidättättätätä		ACAMITERITY OF LANGE CONCOUNTS AND	and and an analysis of the second			apocoapadominamente verse robotal (keep dopis consistenti kila). Fallanda		
ON MAINTENEN CONTRACTOR CONTRACTO		MATERIAL STATES OF THE STATES	SECONOMISSO - SERVINOS DECONOS DECONOCIONOS DE COMPOS DE	independant des la company de la company	Addat rijeloweji ilogoli nake gga sycomows sm	VISSE PER II (1/1-10/4-1-10/2/SEP) PROTECTION OF THE PER INSTITUTE OF TH	TO A SERVICE OF THE PROPERTY O	ampropries of a constant of the contract of th	STEER ST	AND DE LEGEL DE TRES DES PRÉSENTES POR PRÉSENTES PRÉSENTES PRÉSENTES PRÉSENTES PRÉSENTES PRÉSENTES PRÉSENTES P	ausatrastamananevilydespieleitäjä	arse misokalonjajajajajajajajajajajajajajajajajajaja	•	
			HONKIESKIBBIHKKINSKINKERKINKER			MIESTALIA KARININA KARININA DAN KARININA DAN KARININA BARININA BAR	en services sommen parameters and services of	AND	prodosloviji istorija ja prodoslovija je prodoslovija pro					
allokkolonomiskistoisistastaanaasta, tapijiintaja tasuunaasta tahiinta ka	TO SHEET SHE	NATIONAL SANCTON OF THE PROPERTY OF THE PROPER	NEW COLUMN CONTRACTOR	estility of experiments and estility (Charles as expected to the	e e a mandensiament de septembre de la composiçõe de la composiçõe de la composiçõe de la composiçõe de la comp	en a common de la companie de la la companie de la	Marine Marin in Standard return medicine	aggraphe on Guilló (1979) per desente de communità de la cidad de la	eren de des des des des des des des des des	paserenteleuddiauinassessessessessessesenternen	dessinations and an analysis a		delicante de la company de	
	openiera de la companya del companya de la companya del companya de la companya d	Pactorial communications and the communications are communications and the communications and the communications a	non-monthsessessessessessessessessessessessesses	raistayyalkusus-poosopaolysidejtykikky/okonjeunkens	ANNERS STATES OF THE PROPERTY	Estator dissellated dispensioners annual proposition of the second secon	Totaloctocolocics and Selection of Selections of Selection (Selection Selection Select	edocard Acidification of management of the Victoria (Victoria) of	ognemogram isisininin ilgazirinistizzoonna	ander stadentskylljeniperropena taktiskopoblam	Address of the second s	A TO THE	page de la company de la compa	

Table 7. Histopathology

		ylene Öl butyl Et		
Lesions/Dose	High	Inter.	Lov	Control
Testes: Atrophy, seminiferous tubules	0/10	0/10	<b>(</b>	0/10
Epididymides: Degenerated spermatazoa Hypospermia	0/10	0/10		0/10 0/10
Thymus:	0/9	0/10	<b>***</b>	0/10
Stomach: Hyperkeratosis Acanthosis	8/10 1/10		10/10 2/10	0/10
Liver: Hepatocytomegally Anisokaryosis Lack of cytoplasmic	THE CONTROL OF THE CO			0/10 0/10
basophilia				0/10
Spleen: Congestion Red pulp hypocellularity Eemosiderin	6/10 1/10 1/10	0/10 0/10 0/10	(600) (600) (500)	0/10 0/10 0/10
Kidneys: Proximal convoluted tubules, hyaline droplet degeneration Proteinaceous casts Hemosiderin	9/10 9/10 1/10		10/10 1/10 0/10	0/10





DOWANOL® DB: A 5-WEEK REPEATED VAPOR INHALATION STUDY IN RATS.

T. S. Gushow, R. R. Miller, B. L. Yano, and M. J. McKenna. Toxicology Research Lab., Dow Chemical USA, Midland, MI 48640

Male and female Fischer 344 rats were exposed to 0, 2, 6 or 18 ppm DOWANOL DB (diethylene glycol monobutyl ether) for 6 hrs/day, 5 days/wk for 5 weeks. Parameters monitored were clinical observations, body weights, organ weights, hematologic parameters including red cell fragility, urinalysis, clinical chemistry, gross pathology and histopathology.

No treatment-related effects were found in male rats of any exposure group nor in female rats exposed to 2 ppm DOWANOL DB. Slight liver changes in female rats exposed to 6 or 18 ppm were observed. These changes were characterized microscopically as a slightly increased degree of hepatocyte vacuolization consistent with fatty change. Compatible with these microscopic changes, group mean relative liver weights were slightly increased, and paleness of liver was noted grossly in 3 of 10 females in the 18 ppm group. Since a very slight degree of vacuolization (apparent fat accumulation) was observed in the livers of the control and 2 ppm females, the minimal increase of vacuolization observed in the livers of the 6 and 18 ppm females was considered to have questionable toxicological significance. DOWANOL DB does not appear to pose an appreciable inhalation hazard because of its low vapor pressure and minimal toxicologic activity at vapor concentrations which can be attained.

Trademark of The Dow Chemical Company

### **ABSTRACT**

MALE AND FEMALE FISCHER 344 RATS WERE EXPOSED TO

O, 2, 6 OR 18 PPM DOWANOL® DB (DIETHYLENE GLYCOL MONOBUTYL
ETHER) FOR 6 HRS/DAY, 5 DAYS/WK FOR 5 WEEKS. PARAMETERS
MONITORED WERE CLINICAL OBSERVATIONS, BODY WEIGHTS, ORGAN
WEIGHTS, HEMATOLOGIC PARAMETERS INCLUDING RED CELL FRAGILITY,
URINALYSIS, CLINICAL CHEMISTRY, GROSS PATHOLOGY AND
HISTOPATHOLOGY.

NO TREATMENT-RELATED EFFECTS WERE FOUND IN MALE RATS OF ANY EXPOSURE GROUP NOR IN FEMALE RATS EXPOSED TO 2 PPM DOWANOL DB. SLIGHT LIVER CHANGES IN FEMALE RATS EXPOSED TO 6 OR 18 PPM WERE OBSERVED. THESE CHANGES WERE CHARACTERIZED MICROSCOPICALLY AS A SLIGHTLY INCREASED DEGREE OF HEPATOCYTE VACUOLIZATION CONSISTENT WITH FATTY CHANGE, COMPATIBLE WITH THESE MICROSCOPIC CHANGES, GROUP MEAN RELATIVE LIVER WEIGHTS WERE SLIGHTLY INCREASED, AND PALENESS OF LIVER WAS NOTED GROSSLY IN 3 OF 10 FEMALES IN THE 18 PPM GROUP. SINCE A VERY SLIGHT DEGREE OF VACUOLIZATION (APPARENT FAT ACCUMULATION) WAS OBSERVED IN THE LIVERS OF THE CONTROL AND 2 PPM FEMALES. THE MINIMAL INCREASE OF VACUOLIZATION OBSERVED IN THE LIVERS OF THE 6 AND 18 PPM FEMALES WAS CONSIDERED TO HAVE QUESTIONABLE TOXICOLOGICAL SIGNIFICANCE, DOWANOL DB DOES NOT APPEAR TO POSE AN APPRECIABLE INHALATION HAZARD BECAUSE OF ITS LOW VAPOR PRESSURE AND MINIMAL TOXICOLOGIC ACTIVITY AT VOOR CONCENTRATIONS WHICH CAN BE ATTAINED.

### PURPOSE

THE PURPOSE OF THIS STUDY WAS TO EVALUATE THE EFFECTS

OF DOWANOL® DB IN RATS EXPOSED FOR 5 WEEKS AT THE HIGHEST

CONCENTRATION PRACTICALLY ATTAINABLE (APPROXIMATELY 18 PPM),

ALONG WITH 2 LOWER EXPOSURE CONCENTRATIONS (2 AND 6 PPM).

THESE RESULTS WILL BE USED TO HELP ASSESS THE POTENTIAL

HAZARD FROM INHALATION OF DOWANOL DB.

### GENERAL PHYSICAL PROPERTIES

PHYSICAL STATE

MOLECULAR WEIGHT

DENSITY

FLASH POINT (TCC)

BOILING POINT

VAPOR PRESSURE

MOLECULAR FORMULA

STRUCTURE

COLORLESS LIQUID

162.232 G/MOLE

0.955 G/ML

222°F

230°C AT 760 MM Hg

0.03<sup>A</sup> MM HG AT 23°C, 740 MM HG

C8H18O3

 $\mathsf{HOCH_2CH_2OCH_2CH_2CH_2CH_2CH_2CH_3}$ 

### ANALYSIS OF TEST MATERIAL

BOILING RANGE (°C)

H20% WT.

ACID (% AS HAC)

APHA COLOR

SPECIFIC GRAVITY

229.9-232.8

<0.01

0,002

0.953

#### COMPOSITION

DIETHYLENE GLYCOL ISOBUTYLETHER

0.06%

DIETHYLENE GLYCOL

1.3 %

DIETHYLENE GLYCOL N-BUTYL ETHER ~ 98.6 % (BY DIFFERENCE)

NO OTHER IMPURITIES WERE DETECTED ABOVE 300 PPM.

ACALCULATED BY ANTOINE EQUATION

### STUDY DESIGN

ANIMALS

**EXPOSURE CONC** 

**EXPOSURE CHAMBERS** 

PARAMETERS MONITORED

STATISTICAL EVALUATION

15 FISCHER 344 RATS/SEX/CONC.

O, 2, 6 & 18 PPM, 6 HRS/DAY, 5 DAYS/WK FOR 5 WEEKS

157 LITER ROCHESTER-TYPE STAINLESS

STEEL AND GLASS WITH DYNAMIC AIRFLOW

OF 25 LITERS/MIN.

CLINICAL OBSERVATIONS

BODY AND ORGAN WEIGHTS

HEMATOLOGY

RED CELL FRAGILITY

URINALYSIS

CLINICAL CHEMISTRY

GROSS PATHOLOGY

HISTOPATHOLOGY

BARTLETT'S TEST, P < 0.01

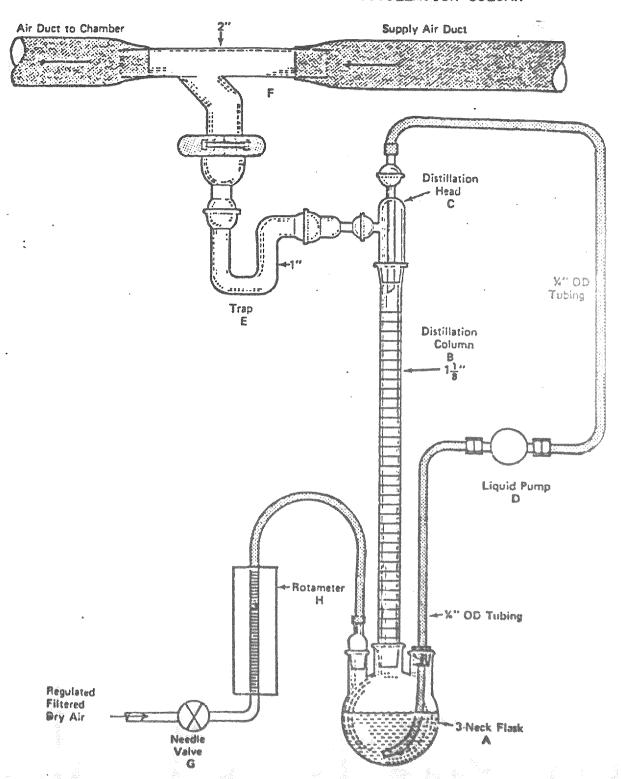
ANALYSIS OF VARIANCE, P < 0.10

DUNNETT'S TEST, P < 0.05

WILCOXON'S TEST, P < 0.05

### VAPOR GENERATION

15-PLATE PERFORATED PLATE DISTILLATION COLUMNA



Apotts, W. J. and Steiner, E. C. (1980). An apparatus for generation of vapors from liquids of low volatility for use in inhalation toxicity studies.

Amer. Ind. Hyg. Assoc. Jl., 41:141-145.

# CHAMBER ATMOSPHERE ANALYSIS

GAS CHROMATOGRAPH

PACKING

COLUMN

COLUMN TEMP

DETECTOR

VARIAN AEROGRAPH 2400

6' X 1/8" STAINLESS STEEL

10% OV-101 ON 80/100 MESH CHROMOSORB W-HP

172°C

H<sub>2</sub> FLAME IONIZATION AT 225°C

### RESULTS

NO EFFECTS IN MALE RATS OF 2, 6, & 18 PPM GROUPS

NO EFFECTS IN FEMALE RATS OF 2 PPM GROUP

MINOR EFFECTS OF QUESTIONABLE TOXICOLOGICAL SIGNIFICANCE IN FEMALE RATS OF 6 & 18 PPM GROUPS

- 1. SLIGHT INCREASE OF HEPATOCYTE VACUOLIZATION CONSISTENT WITH FATTY CHANGE IN 6 & 18 PPM GROUPS OVER THE VERY SLIGHT DEGREE OF VACUOLIZATION OBSERVED IN THE 0 & 2 PPM GROUPS.
- 2. RELATIVE LIVER WEIGHT

  SLIGHT INCREASE IN 6 PPM GROUP

  STATISTICALLY SIGNIFICANT INCREASE
  IN 18 PPM GROUP
- 3. PALENESS OF LIVER IN 3/10 OF 18 PPM GROUP

### LIVER WEIGHTS

	EXPOSURE	•		FASTED BODY	ΓΊΛΕ	R
SEX	LEVEL (PPM)	Special Control of the Control of th		WEIGHT (G)	G <sub>.</sub>	G/100 G
MALE	0	10	MEAN	228.2	7.43	3.26
			±S.D.	8.2	0.44	0.10
	2	10	MEAN ±S.D.	228.8 16.8	7.22 0.69	3.15 0.14
	6	10	MEAN ±S.D.	225.6 15.1	<b>6.</b> 93 <b>0.</b> 69	3.07* 0.14
	18	10	MEAN ±S.D.	227.7 13.3	6.92 0.47	3.04 <b>*</b> 0.06
FEMALE	0	10	MEAN ±S.D.	143.4 5.7	4.02 0.25	2.81
	2		MEAN ±S.D.	140.9 6.7	3.97 0.22	2.82
	6	10	MEAN ±S.D.	140.8 3.5	4.09 0.18	2.91
	18	10	MEAN ±S.D.	138.9 6.1	4.13 0.19	2.98* 0.11

<sup>\*</sup>Significant deviation from control mean using Dunnett's test, P <0.05.

### CONCLUSIONS

DOWANOL® DB IS NOT AN APPRECIABLE INHALATION HAZARD

BECAUSE OF ITS LOW VAPOR PRESSURE AND MINIMAL.

TOXICOLOGIC ACTIVITY AT VAPOR CONCENTRATIONS

WHICH CAN BE ATTAINED.

PREPRINT

RESULTS OF TESTING FIFTEEN GLYCOL ETHERS IN A SHORT-TERM IN VIVO REPRODUCTIVE TOXICITY ASSAY

Ronald L. Schuler\* Bryan D. Hardin\*. Richard W. Niemeier\*

Gary Booth
Minority Enterprise Service Associates
1156 South Street, Suite 105
Orem, Utah 84057

Keith Hazelden
Inveresk Research International, Limited
Edinburgh EH21 7UB, Scotland

Vincent Piccirillo
Borriston Laboratories, Inc.
5050 Beech Place
Temple Hills, Maryland 20748

Kirby Smith
Bioassay Systems Corporation
225 Wildwood Avenue
Woburn, Massachusetts 01801

Department of Health and Human Services\*
U. S. Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Biomedical and Behavioral Science
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, Ohio 45226

Running Head: Short-Term Test of Fifteen Glycols

# RESULTS OF TESTING FIFTEEN GLYCOL ETHERS IN A SHORT-TERM IN VIVO REPRODUCTIVE TOXICITY ASSAY

Ronald L. Schuler
Bryan D. Hardin :
Richard W. Niemeier
Gary Booth
Keith Hazelden
Vincent Piccirillo
Kirby Smith

#### KEY WORDS

Reproductive toxicity, teratology, screen, glycols, and glycol ethers

#### ACKNOWLEDGMENTS

The authors wish to express their appreciation to Sandra Clark (NIOSH) for the excellent typing of this manuscript.

## RESULTS OF TESTING FIFTEEN GLYCOL ETHERS IN A SHORT-TERM IN VIVO REPRODUCTIVE TOXICITY ASSAY

#### **ABSTRACT**

reproductive toxic effects using an <u>in vivo</u> mouse, screening bioassay.

Pregnant mice were orally dosed once per day on days 7 through 14 of gestation at concentrations causing 0 to 41 percent maternal mortality. Reproductive endpoints included pup survival <u>in utero</u> (percent of live litters/pregnant survivors), pup perinatal and postnatal survival (number of live pups per litter, number of dead pups per litter, and pup survival to 2.5 days of age), and pup body weight statistics (weight at birth and weight at 2.5 days of age).

The study was conducted in two phases: a dose range-finding phase using non-pregnant female mice, and a definitive reproductive phase using time-mated mice. The range-finding phase sought to identify, for each chemical, the maternal  $\mathrm{LD}_{10}$  as the target dose. However, based upon reproductive phase results, such an exact dose was impractical to achieve. Thus, a range from the  $\mathrm{LD}_{5}$  to the  $\mathrm{LD}_{20}$  was considered a sufficient challenge dose that would not affect results due to high mortality, i.e., greater than the  $\mathrm{LD}_{20}$ .

Glycol ethers were assigned to groups having different priorities for further testing based upon whether a sufficient challenge dose was administered and the degree of effects recorded for each chemical. These groups and chemicals are: a) very high priority--triethylene glycol dimethyl ether (TriEGdiME); b) high priority--ethylene glycol (EG), ethylene glycol monomethyl ether (EGME), ethylene glycol monomethyl ether (EGME), ethylene glycol diethyl ether (EGdiEE), and diethylene glycol monomethyl ether (DiEGME); c) middle to high priority--ethylene glycol dimethyl ether (EGdiME) and diethylene glycol dimethyl ether (DiEGdiME); d) middle priority--ethylene glycol monobutyl ether (EGBE), diethylene glycol (DiEG), diethylene glycol diethyl ether (DiEGdiEE) and triethylene glycol (TriEG); e) low priority--diethylene glycol monoethyl ether (DiEGEE) and diethylene glycol dibutyl ether (DiEGdiBE). Diethylene glycol monobutyl ether (DiEGBE) was not administered at a sufficient challenge dose and should be repeated.

NIOSH does not regard these results as appropriate for labeling a compound as safe or unsafe. Instead they are suggestive, when considered along with other information on each chemical, of the urgency with which these chemicals should be considered for more detailed conventional testing.

#### DITRODUCTION

Conventional reproductive testing is expensive, involves complex scheduling, and requires the commitment of highly trained personnel. These intricate requirements, coupled with the existence of a large number of compounds that lack reproductive toxicity information, have created an urgent need for rapid, inexpensive methods of screening chemicals for reproductive toxicity. With this in mind, the National Institute for Occupational Safety and Health (NIOSH), in conjunction with the National Toxicology Program (NTP) in 1981 pegan to evaluate an in vivo screening test developed by Chernoff and Kavlock (1). For this test, pregnant mice are treated during organogenesis with high doses of the test chemicals. Females are then allowed to deliver their litters and the number of live-born pups, their birth weight, and growth and survival to 2-3 days of age are monitored. While the test is not appropriate for labeling a compound as safe or unsafe, it may serve to generate data useful in establishing priorities for conventional testing. It may also be useful for rapidly surveying structure-activity relationships. As part of the NTP evaluation of potential reproductive toxins, four contracts were awarded by NIOSH under which a total of 30 chemicals were tested. Fifteen of the chemicals were glycols or glycol ethers and the results of those tests are summarized here. Of these fifteen, three contractors tested four chemicals each and one contractor tested the remaining three (see Table 1). None were tested in more than one laboratory.

All contractors used CD-1 mice purchased from Charles River Breeding
Laboratories, Inc. (Wilmington, Massachusetts) throughout these studies.

Chemicals were evaluated in two phases: a preliminary dose-finding study in nonpreynant mice followed by the reproductive phase using time-mated females.

In both phases chemicals were evaluated in blocks of 2 to 4 chemicals with a snared concurrent vehicle control group. Some blocks included only glycols, others included other chemicals. Only data on glycols are reported here.

Chemicals were provided to contractors by NIOSH and were tested in blind, with the chemicals identified by an arbitrary code number. Table 1 summarizes the glycols tested and their abbreviations, structural formulas, chemical purity, and the laboratories that performed the investigations. DiEGdiBE was administered in corn oil due to its insolubility in water. Distilled water served as the vehicle for all other glycols tested. Dosage was by oral gavage in all instances.

The dose range-finding study was conducted at 5 dose levels using 10 mice, 6 to 8 weeks old, per treated or control group (except for diEGBE and diEGdiEE where the mice were 60 to 80 days old 1). Upon receipt, mice were weighed and marked for individual identification, then formally randomized to treatment groups. Mice were group-housed, 5 per cage throughout the range-finding study. Standard laboratory rodent chow and untreated tap water were available ad libitum. Bedding of a type known not to induce microsomal enzymes was changed as needed or at least once per week. Oral doses were administered once daily for 8 consecutive days using a constant dose volume of

10 ml/kg body weight. Body weights were recorded on days 1 and 8 of the dosing period and on days 4 and 8 of an 8-day post-dosing observation period. Group mean or individual body weights taken on the first day of dosing were used to calculate treatment volumes over the entire 8-day dosing period. Survivors were sacrificed immediately following the last weighing on the 8th post-dosing day. All mice that died before that time were necropsied for evidence of dosing error as a cause of death. Based on the results of these dose-finding studies, the estimated LD<sub>10</sub> dose was selected for the reproductive phase.

Reproductive studies were conducted in time-mated CD-1 mice, 6 to 8 weeks of age, orally dosed on days 7 to 14 of gestation (day 1 of gestation is the day on which a copulatory plug is observed). Mice were received on or before day 5 of gestation. On day 5 they were weighed and marked for individual identification, then formally randomized to treatment or control groups of 50 mice each. Test chemicals were administered at a single dose in a constant volume of 10 ml/kg body weight. Maternal body weights were taken on day 7 of gestation immediately before dosing, on day 18 of gestation, and on day 3 postpartum. The weight of the animal on gestation day 7 was used to calculate the dosage for the entire period. All mice were housed individually throughout the reproductive study. Food, water and bedding were provided as in the range-finding studies except bedding was not changed after gestation day 18.

Females were observed with minimal disturbances twice daily beginning on day 18 of gestation. As soon as possible after litters were delivered (within 12

hours), the number of live and still-born pups was recorded. Maternal body weight was recorded and all live pups were weighed together. Pups and their dams were then returned to nest boxes and were left undisturbed until 48 hours after the initial weighing, at which time the number of live pups, their total weight, and maternal body weight were again recorded.

Details of the statistical analyses varied from one contractor to another, but generally the procedures were similar. Body weight data were analyzed by analysis of variance. The proportion of surviving pregnant mice that gave birth to viable litters (1 or more live-born pups) was evaluated by the Fisher-Irwin Exact test. Numbers of live and still-born pups and percent survival to 2.5 days of age were analyzed by analysis of variance and the Student's t-Test.

#### RESULTS

Table 2 and Table 3 present the findings of the postnatal screen of the 15 glycol ethers. Because these chemicals were investigated by four independent laboratories at different times, and in some cases concurrently with other chemicals, seven control groups were used (some controls served more than one chemical). Control values were generally consistent across these seven groups. There was only one maternal death in all control groups and that was a result of a gavage error. Reproductive success in the controls ranged from 91 percent to 100 percent of all pregnant survivors. The average litter size ranged from 9 to 11 pups per litter. The percent pup postnatal survival (to 2.5 days postpartum) ranged from 98 to 100 percent. The average pup weight gain over days 1 to 3 postpartum ranged from 0.4 g to 1.1 g and the average pup birth weight ranged from 1.6 g to 1.7 g.

Nine of fifteen glycols tested affected the viable litter index. Pregnant mice treated with EGME, EGEE, EGdiME, diEGdiME, and triEGdiME produced no viable litters. Mice treated with EG, EGBE, EGdiEE and diEGME showed a significant reduction (p<0.05) in viable litters produced (41, 77, 11, and 16 percent viable litters produced, respectively). The remaining glycols and glycol ethers produced no effect on that reproductive index at the concentrations administered.

Postnatal observations varied widely in those groups with viable litters. EG and EGdiEE reduced the number of live pups per litter, increased the number of dead pups per litter, reduced pup survival, reduced pup birth weight, and reduced pup weight gain over days 1 to 3 postpartum. EGdiEE data were not analyzed statistically because of the small sample size. DiEGME significantly reduced (p<0.05) the number of live pups per litter and pup survival over days 1 to 3 postpartum. DiEGdiEE significantly increased (p<0.05) the number of dead pups per litter and significantly reduced (p<0.05) pup birth weight.

DiEGdiBE increased (p<0.05) the number of dead pups per litter. DiEG reduced (p<0.05) pup weight gain over day 1 to 3 postpartum and triEG and diEGEE reduced (p<0.05) mean pup birth weight.

#### DISCUSSION

Because it is our intent to use this bioassay to screen chemicals for their potential to cause reproductive toxicity in pregnant females, it is necessary to employ clearly toxic doses. If a chemical is evaluated as a low priority, one wants to be relatively confident that it was tested at a sufficiently

severe challenge level. Clear maternal toxicity does not mean that reproductive toxicity follows. DiEG and triEG produced 4 percent maternal mortality; diEGdiBE produced 8 percent mortality; and diEGEE produced 14 percent mortality. None of these showed strong evidence of reproductive toxicity. In fact, diEGEE treatment did not adversely affect any of the reproductive indices.

As noted, the estimated maternal LD $_{10}$  was chosen as the challenge dose to be used for the reproductive studies. In practice, mortality will vary somewhat, and a response in the LD $_{5-20}$  range was considered acceptable in the reproductive phase. If reproductive effects are noted in the presence of more than 20 $_{\Delta}$  maternal initiality, the test probably should be repeated at a lower dose. Conversely, if there is no reproductive toxicity and less than  $5_{\Delta}$  maternal mortality, the test probably should be repeated at a higher dose. This LD $_{5-20}$  range, however, is only a tentative suggestion and further experience with this test may suggest other criteria for judging the appropriateness of the challenge dose.

The six endpoints examined for determining the priority of chemicals for further testing can be condensed into three levels of consideration. Most important is pup survival in utero, i.e., percent viable litters delivered by pregnant survivors. Of second importance is pup perinatal and postnatal survival, i.e., the number of live and dead pups per litter at birth, and pup survival over days 1-3 post partum. Final consideration is given to pup body weight endpoints, i.e., pup weight gain over days 1-3 and pup weight at birth.

Chemicals were assigned to groups having different priorities for further testing based upon whether a sufficient dose was administered (the maternal LD<sub>5-20</sub>) and the degree of effects recorded for each chemical. TriEGdiME therefore has a very high priority for further testing because the administered dose of 4 percent maternal mortality was less than the  $LD_{5-20}$ and the results were profound, i.e., no viable litters delivered. Other chemicals deserving high priority include EG, EGME, EGEE, EGdiEE, and diEGME in that all were tested within the range of 5-20 percent maternal mortality and all showed a drastic reduction of viable litters. A middle to high level priority group would include EGdiME and diEGdiME because both produced no viable litters but they received a dose greater than the LD5-20 which could have influenced the results due to maternal toxicity effects. A middle level priority group would include EGBE, diEG, diEGdiEE and triEG. EGBE significantly reduced viable litters with no other effects when dosed at the upper limit of the range of acceptable mortality. DiEG, diEGdiEE and triEG mice received less than the LD<sub>5-20</sub> dose but still produced some lesser effects: reduced pup weight gain for diEG; reduced pup weight gain and decreased number of live pups per litter for triEG; and an increased number of dead pups per litter plus a reduced pup birth weight for diEGdiEE. A low priority group would include diEGEE and diEGdiBE because the LD 5-20 dose was achieved and only lesser effects were seen, i.e., a reduced pup birth weight for diEGEE and an increased number of dead pups per litter for diEGdiBE. DiEGBE mice did not receive a maternally toxic dose and no effects were found, thus dieGBE should be repeated until an  $LD_{5-20}$  dose is achieved.

It is important to note that, for the purposes of this screen, comparisons among chemicals are based upon maternal mortality, i.e., doses less than, greater than, or within the  $LD_{5-20}$  range. Comparisons as to the potential exposure hazard are not made. For example, although EG is designated to a higher priority group than EGBE, it may be that an individual is more likely to receive an 1,180 mg/kg dose of EGBE ( $LD_{20}$ ) than he is to receive an 11,090 mg/kg dose of EG ( $LD_{10}$ ). Thus EGBE may be more of a potential hazard than EG.

Previous investigations have shown several of the glycol ethers assessed in the current work to be teratogenic in traditional teratology test systems.

EGME (designated in our high priority group) induced skeletal anomalies in the offspring of mice receiving, by oral gavage, as low as 31 mg/kg/day over days 7 through 14 of gestation (2). Gross (external) anomalies and the incidence of embryonic death were greatly increased in the offspring of mice receiving 250 mg/kg/day. In an inhalation study, 200 ppm EGME for 7 hours/day on gestation days 7 through 15 caused complete embryonic death in rats (3).

Reduced fetal weights, skeletal and cardiovascular defects, as well as increased embryonic death occurred at both 50 and 100 ppm.

embryonic death, and decreased pup weight in offspring of rats treated by oral gavage on days 1 through 21 of gestation (4). Doses ranged from 12 to 327 mg/kg/day. Inhalation of 160 ppm EGEE for 7 hours/day on days 1 through 18 of gestation increased embryonic death and skeletal anomalies in rabbits (5). At 615 ppm complete embryonic death occurred. Offspring of rats receiving a 1.0 ml or 2.0 ml dermal application of EGEE on days 7 through 16 of gestation

showed greatly increased embryonic deaths, and cardiovascular and skeletal anomalies (2). Offspring of rats receiving 100 ppm of EGEE for 7 hours/day on days 7 through 13 or 14 through 20 of gestation showed altered behavioral patterns and altered brain neurochemical concentrations (7).

EGdiME, placed in our middle to high level priority group, administered to pregnant mice by oral gavage on days 7 through 10 of gestation caused increased embryonic death at concentrations of 250, 350, and 490 mg/kg/day (8). Skeletal and external anomalies occurred in the 490 mg/kg group. EGBE, in our middle priority group, caused no apparent adverse effect on the offspring of rats exposed to 200 ppm EGBE for 7 hours/day on gestation days 7 through 15 (3). DiEGEE, in our low priority group, caused no adverse effect on the offspring of rats exposed to 100 ppm for 7 hours/day on days 7 through 15 of gestation (3).

Some general statements can be made regarding structure activity relationships (Table 4). All mice receiving glycol ethers having terminal methyl groups, i.e., EGME, EGdiME, diEGME, diEGdiME, and triEGdiME produced few viable litters (0, 0, 16, 0, and 0 percent, respectively). Only EGEE and EGdiEE having terminal ethyl groups produced similar results (0 and 11 percent viable litters, respectively). The remaining ethyl ethers (diEGEE and diEGdiEE), the butyl ethers (EGBE, diEGBE, diEGdiBE), and the glycol ethers with terminal hydroxy groups (EG, diEG and triEG) did not produce such profound fetotoxicity. Maternal toxicity of the glycols was sharply increased by the addition of an alkyl group. EGBE was more toxic than EGME which was more toxic than EGEE. All three showed greater toxicity than EG. The diEG mono-

and diEGdi-alkyl ethers were more toxic than diEG, and triEGdiME was more toxic than triEG. The methyl ethers were generally more toxic than the ethyl or butyl ethers with the exception of EGBE.

We would caution again that neither NIOSH nor the NTP regard these results as definitive. Instead, they are suggestive, when considered along with other information on each chemical, of the urgency with which these chemicals should be considered for more detailed conventional testing. From the current available information on the glycol ethers, a correlation can be seen between the known positive teratogens (EGME, EGEE and EGdiME) and their results in this in vivo screen where these compounds were designated either in a high priority or middle to high priority group. Also, EGBE and diEGEE, which showed no reproductive toxicity in conventional tests, were given a lower priority ranking (middle or low group) following testing in this screen.

#### REFERENCES

- 1. Chernoff, N., and Kavlock, R. J. An in vivo teratology screen utilizing pregnant mice. J. Toxicol. Environ. Health 10:541-550 (1982).
- 2. Jagano, K., Nakayama, E., Oobayashi, H., Yamada, T., Adachi, H., Aishizawa, T., Ozawa, H., Nakaichi, M., Okuda, H., Minami, K., and Yamazaki, K. Embryotoxic effects of ethylene glycol monomethyl ether in mice. Toxicology 20:335-343 (1981).
- 3. Nelson, B. K., Setzer, J. V., Brightwell, W. S., Mathinos, P. R., Kuczuk, M. H., Weaver, T. E., and Goad, P. T. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. Environ. Hith. Perspect. (in press).
- Stanger, E. G., Aeppli, L., Muller, D., Peheim, E., and Thomann, P. The toxicology of ethylene glycol monoethyl ether. Arzneim. Forsch.
   21:880-885 (1971).
- 5. Andrew, F. D., Buschbom, R. L., Cannon, W. C., Miller, R. A., Montgomery, L. F., Phelps, D. W., and Sikov, M. R. Teratologic assessment of ethylbenzene and 2-ethoxyethanol. NIOSH contract report. Battelle Pacific Northwest Laboratory, Richland, WA, 99 pp (1981).
- 6. Hardin, B. D., Niemeier, R. W., Kuczuk, M. H., Mathinos, P. R., and Weaver, T. E. Teratogenicity of 2-ethoxyethanol by dermal application.

  Drug Chem. Toxicol. 5(3):277-294 (1982).

Heurotoxicology 2:231-249 (1981).

8. Uermura, K. The teratogenic effects of ethylene glycol dimethyl ether on the mouse. Acta Obstet. Gynaec. Jpn. 32(1):113-121 (1980).

#### FOOTHOTES

 Because of the demand placed upon the single animal supplier by all four contractors, the initial requirement to use 60 to 80 day old mice was changed. This change required the use of the more readily available 6 to 8 week old mice.

Glycol Ethers Investigated

Contractors*	Inveresk Bioassay MESA Bioassay Borriston Bioassay	Inveresk Bioassay MESA Borriston MESA Borriston Inveresk	Borriston MESA
Percent Purity	\$ 8 \$ 8 \$ \$ \$ 8 \$ 8 \$ \$	788888	88
Empirical		C403H10 C503H14 C603H14 C803H18 C803H18 C1203H26	Ceden14 Ceden14
Formula	HO-Et-OH Me-O-Et-OH Ne-O-Et-O-Me Et-O-Et-OH Et-O-Et-OH	HO-Et-O-Et-OM Me-O-Et-O-Et-OM Et-O-Et-O-Et-OM Et-O-Et-O-Et-OM Bu-O-Et-O-Et-OM Bu-O-Et-O-Et-OM	HO-Et-O-Et-O-Et-OH: Me-O-Et-O-Et-O-Et-O-Ne
61ycol	thylene Glycol (EG)  thylene Glycol Monomethyl Ether (EGNE)  thylene Glycol Dimethyl Ether (EGGINE)  thylene Glycol Monoethyl Ether (EGEE)  thylene Glycol Diethyl Ether (EGGIEE)  thylene Glycol Monobutyl Ether (EGBE)	dethylene Glycol (dfEG) dethylene Glycol Monomethyl Ether (diEGdiNE) dethylene Glycol Monoethyl Ether (diEGEE) dethylene Glycol Monoethyl Ether (diEGEE) dethylene Glycol Monobutyl Ether (diEGEE) dethylene Glycol Monobutyl Ether (diEGGIEE) dethylene Glycol Dibutyl Ether (diEGGIE)	riethylene Glycol (triEG) Ether (triEGdiME)

Bloassay Systems Corporation, 225 Wildwood Avenue, Woburn, Massachusetts 01801
Borriston Laboratories, Incorporated, 5050 Beech Place, Temple Hills, Maryland '20748
Inverest Research International Limited, Edinburgh EH21 70B, Scotland
Mimority Enterprise Service Associates, 1156 South State, Orem, Utah 84057

Glycol Ethers Results
Maternal Mortality and Pregnancy Success

Block	<u>Glycol</u>	Dose (mmo1/kg)	Property.	Maternala Mortality (Percent)	Yiable <sup>b</sup> Litters (Percent)
. A	Control ECME EGZE EGBE d1EGME	18.4 40.1 10.0 33.3	1400 3605 1180 4000	0/50 (.0) 7/49 (14) 5/50 (10) 10/50 (20) 5/50 (10)	31/32 ( 97) 0/30* ( 0) 0/32* ( 0) 24/31* ( 77) 5/32* ( 16)
8	Control diEG8E	3.1	<b>5</b> 00	0/49 ( 0) 0/50 ( 0)	30/31 ( 97) 36/37 ( 97)
C	Control EGdiEE diEGEE triEGC	25.0 41.0 75.1	2955 5500 11270	0/50 ( 0) 5/50 (10) 7/50 (14) 2/50 ( 4)	42/42 (100) 4/35* (11) 32/33 (97) 36/36 (100)
D	Control EGC diEGC	178.9 105.5	11090 11180	0/50 ( 0) 5/50 (10) 2/50 ( 4)	29/29 (100) 15/37* (41) 33/36 (92)
E	Controld diEGdiBEd	9.2	2000	0/50 ( 0) 4/50 ( 8)	<b>45/45</b> (100) <b>38/40</b> (95)
F	Control diEGdiEE	18.5	3000	0/50 ( 0) 0/40 ( 0)	41/45 ( 91) 35/41 ( 85)
G	Control EGdiME diEGdiME triEGdiME	22.2 22.4 19.7	2000 3000 3500	0/50 ( 0) 13/50 (26) 20/49 (41) 2/50 ( 4)	42/43 ( 98) 0/34* ( 0) 0/27* ( 0) 0/37* ( 0)

a Treatment-related deaths/number on test (percent mortality)
b Litters with 1 or more live-born pups/number of pregnant survivors

<sup>(</sup>percent of pregnancies)

G Administered without dilution in volume of 10 ml/kg

d Corn oil used as the vehicle--all other groups used distilled water vehicle # Differs significantly (p<0.05) from concurrent control by Fishers Exact Test

Pup Birth Veight (g)	9.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1	1.6	1.544	1.7	1.5	1.6
Weight Gain (g) Over Days 1-3 Post Partum	4.00.00	1.1	1.0 0.2*** 0.6***	. 9.0		2.0
Percent Pup Postnatal Survival	100 - 95 31*	99 99 99 \$54 \$4	100 100 100 100 100 100 100 100 100 100	88	86	
No. Dead Pups Per Litter At Birth	0.1	00 00	0.1	00	- * - • •	
Live Pups Per Litter At Birth	10 litters no litters 10	99 91 99	6 620		99	no litters of litters
[63/ <u>(68)</u>	1400 3605 11180 4000	500 2955 5500	11270	. 2000	3000	3000
Dose (mmo1/kg.)	3.00 3.00 3.00 5.00	3.1 25.0 41.0	75.1 178.9 105.5	9.2		22.2 22.4 19.7
Glycol	Control EGNE EGE EGE EGDE diEGNE	Control discass control scaling discass	tries Control Es dies	Control digGdIBE	Control	Control Ecding diecding triecding

Significantly different (p.0.05) from concurrent control by analysis of variance of tested statistically due to small sample size statistically due to small sample size size statistically different (p.0.05) from concurrent control by Student's t-Test

### CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

Data produced 10 7 87 Bouleau Smith
(Month) (Day) (Year) Camera Operator

Place Syracuse New York
(City) (State)

